

LETTERS

Multiple painful sensory mononeuropathies (MPSM), a novel pattern of sarcoid neuropathy

Sarcoidosis is a granulomatous disease with the potential to affect many different organ systems. Approximately 5% of patients with systemic sarcoidosis have neurological involvement.¹ Peripheral neuropathy occurs in up to 20% of these patients and is usually asymptomatic. Neurophysiological findings are consistent with primary axonal polyneuropathy.¹ We report an unusual case of neurosarcoidosis, presenting with multiple painful sensory mononeuropathies (MPSM) and progressing to a symmetric confluent sensory neuropathy.

Case report

A patient in her 4th decade of life presented with a history of multiple sensory deficits. She first developed acute onset pain and numbness of the right little finger, followed by a change in taste over the anterior two thirds of the tongue, without facial weakness. Two months later, the patient developed numbness in the palmar aspect of all fingers with dysesthesia, intermittent burning, and throbbing pain. Three months later, the pain spread to involve the dorsal aspect of the forearms. Seven months after the initial onset of symptoms, the patient developed a burning sensation in the distribution of the right sural nerve, and numbness in the right posterior leg and over the left side of the trunk. The patient denied muscle weakness, painful radicular symptoms, or systemic features.

Physical examination was remarkable for the absence of sweet taste sensation over the anterior tongue bilaterally. Sensory examination demonstrated reduced pinprick sensation in the fingers of both hands and in the right sural nerve distribution. Muscle strength was preserved throughout. Tendon reflexes were absent in the arms and ankles, and asymmetric at the knees. Gait, cognitive functions, and cranial nerve examination were unremarkable.

Laboratory investigations included a polyclonal increase in IgGM component, with a low concentration band in the slow γ region. Serum immunofixation confirmed the presence of IgG λ . Serum antineutrophil antibodies were positive, with a homogeneous pattern (1/640), and the serum angiotensin converting enzyme (ACE) concentration was raised (69 U/litre; normal range, 8–52). Other laboratory investigations were normal or absent, including serum chemistry, complete blood count, erythrocyte sedimentation rate, serum vitamin B12 concentration, antinuclear antibodies, anti-SSA/SSB antibodies, rheumatoid factor, cryoglobulins, serum complement, and serology testing for Epstein-Barr virus, herpes simplex virus types 1 and 2, and human immunodeficiency virus types 1 and 2. Cerebrospinal fluid (CSF) examination revealed an increased concentration of protein (980 mg/litre; normal range, 150–450), with oligoclonal bands. The CSF cell count, bacterial culture, Gram stain, Lyme antibody titre, and myelin basic protein were unremarkable. Nerve conduction studies

(NCSs) revealed absent right sural, right superficial peroneal, and bilateral ulnar and median sensory nerve action potentials (SNAPs). The remainder of the motor and sensory NCSs and needle electromyography, in the upper and lower extremities, were unremarkable. Blink reflexes were normal. Median nerve somatosensory evoked potential study revealed absent Erb's point potentials, bilaterally. Follow up NCSs, three months after the initial study, showed deterioration in the sensory NCSs, as demonstrated by the loss of left sural, left superficial peroneal, and both radial SNAPs. The sensory neuropathy had now become confluent and symmetrical. Motor NCSs remained normal. Non-contrast brain magnetic resonance imaging demonstrated three small subcortical white matter signal changes. Chest x ray was normal. A chest computerised tomography scan demonstrated scattered centrilobular nodules, with thickening of the interlobular septa, and no hilar lymphadenopathy, which was consistent with lung sarcoidosis. Pulmonary function tests were normal. Abdominal fat pad aspiration biopsy was negative for amyloid. A right sural nerve biopsy revealed non-caseating granulomas admixed with chronic inflammatory cells in the epineurium (fig 1A, B). Immunohistochemistry of the lymphoid infiltrate was not possible because of technical difficulties. Sural nerve teased fibre preparations revealed myelin ovoids in numerous fascicles. Vasculitis was not seen. Biopsy of the right gastrocnemius muscle was normal. The patient was treated with prednisone, starting at 60 mg/day. At last follow up, 12 months after treatment onset, the patient continued to experience pain, but had not developed new neurological deficits. The patient was eventually lost to follow up.

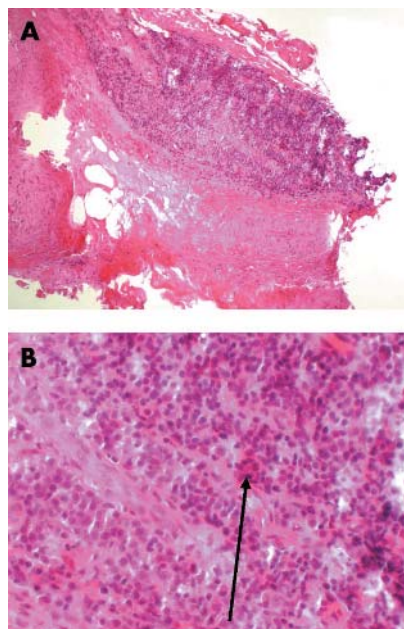


Figure 1 (A, B) Haematoxylin and eosin stained section of the right sural nerve, at different magnifications, demonstrating a prominent collection of epithelioid histiocytes admixed with chronic inflammatory cells in the epineurium; (A) original magnification, $\times 100$; (B) original magnification, $\times 400$. The arrow in (B) indicates a multinucleated giant cell.

Discussion

We report a case of sarcoid neuropathy presenting as MPSM and progressing to a symmetric confluent sensory polyneuropathy. This case was particularly challenging because the patient was not known to have sarcoidosis at presentation. The findings of a raised serum ACE concentration and lung computerised tomography imaging suggested a diagnosis of sarcoidosis. This was confirmed by demonstrating non-caseating granulomas in the epineurium of the right sural nerve. Although previous cases of pure sensory sarcoid neuropathy have been reported, they were distinct from our case in that the patients were already diagnosed with systemic sarcoidosis,² or the symptom of pain was unreported.² To our knowledge, our case is the first description of systemic sarcoidosis presenting as MPSM.

Sensorimotor and pure motor polyneuropathies have been reported in systemic sarcoidosis.^{1,2} The relative frequency of different subtypes of sarcoid neuropathies is uncertain. In a detailed clinical description of 10 cases, chronic sensorimotor peripheral neuropathy was the most common form of non-cranial neuropathy.¹ Other patterns included small fibre neuropathy,³ acute ascending paralysis similar to Guillain-Barré syndrome,¹ polyradiculopathy,⁴ and lumbosacral plexopathy.¹

A potential mechanism of nerve damage in sarcoid neuropathy includes the local effects of tissue inflammation through release of noxious secretory products by activated inflammatory cells.⁵ Alternatively, ischaemia induced by necrotising vasculitis⁵ and direct mechanical compression of nerve fibres may lead to primary axonal degeneration,² as supported by pathological findings of non-caseating granulomas in the epineurium and perineurium with periangiitis, panangiitis, perineuritis, and axonal loss.⁵ Furthermore, most neurophysiological findings were consistent with an axonal form of nerve injury.^{1,2} In our case, the neurophysiological and pathological findings were consistent with primary axonal degeneration. We hypothesise that peripheral nerve injury may have resulted from mechanical compression of nerve fibres, because there was no evidence of vasculitis in our case. Moreover, the effects of local tissue inflammation could not be ruled out in this case.

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M Dreyer

Neurological Consultants PC, Suite 210, 140 Hospital Drive, Bennington, Vermont 05210, USA

S Vucic, D P Cros, P Siao Tick Chong

Department of Neurology, Bigelow 1256, Massachusetts General Hospital, 55 Fruit St, Boston, 02114, MA, USA; PSIAO@PARTNERS.ORG

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Non-herpetic limbic encephalitis associated with relapsing polycondritis

Relapsing polycondritis is a generalised disorder characterised by recurrent inflammation of cartilaginous structures throughout the body, without recognised collagen disease or infectious disorders. Central nervous system involvement is rarely reported in this disorder. We describe the cases of two patients with relapsing polycondritis who presented with severe memory impairment and psychiatric features such as euphoria and hyperactive behaviours, leading to a diagnosis of non-herpetic limbic encephalitis.

Limbic encephalitis is caused by the herpes simplex virus (HSV) or by heterogeneous non-herpetic disorders (non-herpetic viruses, Hashimoto's encephalopathy, central nervous system lupus, gliomatosis cerebri, intravascular malignant lymphomatosis, and paraneoplastic conditions). Clinical characteristics include cognitive dysfunction, severe memory impairment, seizures, depression, anxiety, and hallucinations. Magnetic resonance imaging (MRI) studies reveal selective unilateral or bilateral involvement of the limbic system, particularly the medial temporal lobe regions.

Our first patient was a 45 year old man referred to us because of subacute progressive mental confusion, euphoria, hyperactive behaviour, disorientation, and forgetfulness of recent episodes. He had a history of right sided conjunctivitis successfully treated with steroid and antibiotic ointment, shoulder stiffness, headache, low grade fever, and recent weight loss (6 kg).

On admission, the patient was disoriented, with an inappropriately jocular affect, disjointed speech, confabulation, attention deficits, and memory impairment including anterograde and 1 year retrograde amnesia. His Mini Mental Status Examination (MMSE) score was 11 (of a possible 30). He had no pyramidal or extrapyramidal disturbances or cerebellar ataxia. T2 weighted MRI showed bilateral, small, disseminated high intensity signals in the medial temporal lobe, hippocampus, and insular cortex (fig 1A).

Laboratory studies showed white blood cell count $14.8 \times 10^9/l$ (normal $3.9-9.3 \times 10^9/l$), platelet count $363 \times 10^9/l$, β -thromboglobulin (β -TG) $94 \mu g/l$ (normal $<50 \mu g/l$), platelet factor 4 (PF-4) 30 ng/ml (normal $<20 \text{ ng/ml}$), erythrocyte sedimentation rate (ESR) 42 mm/h , C reactive protein (CRP) 29 mg/l , ferritin $668 \mu g/l$ (normal $<465 \text{ ng/ml}$), rheumatoid factor 145 IU/ml (normal <20), and antinuclear antibodies (ANA) 1:40. Serum tests were negative for myeloperoxidase antineutrophil cytoplasmic antibodies, anti-DNA, anti-SSA/SSB, and anti-RNP. Thyroid function and vitamin B₁ and B₁₂ levels were normal. Syphilis, HSV-1, HSV-2, herpes zoster virus, human herpes virus 6, cytomegalovirus, Epstein-Barr virus, measles, rubella, and mumps were serologically excluded. No neoplasm was detected. Cerebrospinal fluid (CSF) was sterile, with a protein concentration of 86 mg/dl ; glucose, 3.0 mmol/l (serum glucose, 5.5 mmol/l);

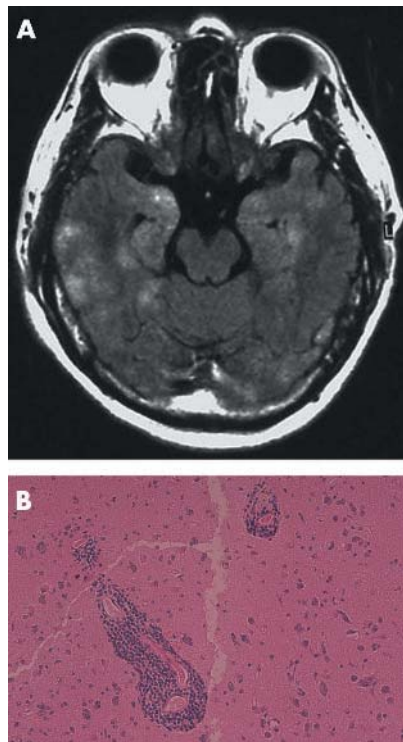


Figure 1 (A) Brain magnetic resonance imaging (MRI) in patient 1. Fluid attenuated inversion recovery imaging showed bilateral, small disseminated high-intensity signals in the medial temporal lobe (original magnification $\times 48$). (B) Brain biopsies from the right temporal lobe of patient 1 showed perivascular cuffing and vascular wall thickness. Haematoxylin-eosin staining.

white cells, $8 \times 10^9/l$ (94% lymphocytes); and IgG/albumin index, 1.02.

Despite intravenous acyclovir, his cognitive function deteriorated, and his MMSE score decreased to 4. He developed right conjunctivitis, left wrist pain, and bilateral auricular swelling. Brain biopsy showed marked gliosis with scattered gemistocytic astrocytes, perivascular cuffing, and destruction of the vascular wall (fig 1B). After high dose intravenous methylprednisone, then 40 mg oral prednisone per day, his psychiatric and cognitive functions improved dramatically and the joint pain and auricular swelling disappeared. Mild impairment of recent memory and orientation remained. MRI performed 1 month later revealed bilateral cortical atrophy in the temporal lobes with dilated temporal horns.

Our second patient was a 62 year old man who presented with subtle memory impairment, confusion, and euphoria, with a history of ankle and wrist pain. On examination, he had mild hearing loss and bilateral auricular swelling. Although appearing alert and happy, he had amnesic episodes, was disoriented, and had impairment of memory storage and calculation (MMSE score 4). He followed simple commands, but filled in memory gaps with inaccurate and implausible information. All other neurological findings were unremarkable.

Laboratory examination showed ESR 20 mm/h , CRP 12 mg/l , IgE 1570 IU/l , fibrinogen 5.51 g/l , and ferritin $448 \mu g/l$. Thyroid

function and serum vitamin B₁ and B₁₂ levels were normal. Results were negative for all bacterial, mycobacterial, fungal, and viral stains and cultures, and for specific antigen tests. Whole body computed tomography and gallium scintigrams to search for neoplasms in the lungs, thymus, and testis and for haematological malignancies yielded negative results. CSF examination showed increased white cell count $24 \times 10^9/l$ (83% lymphocytes), protein 46 g/l , glucose 4.27 mmol/l (serum glucose 5.94 mmol/l), and IgG/albumin index 1.56 (normal <0.6).

Fluid attenuated inversion recovery (FLAIR) images and T2 weighted MRI revealed bilateral, sparse, high intensity patches in the mediotemporal lobe, including the insula, hippocampus, and amygdala, and abnormal signals in the deep white matter. Auricular biopsy showed active chondritis. Brain biopsy demonstrated prominent perivascular cuffing around the meningeal and intracerebral vessels with increased vascular wall thickness.

After methylprednisone pulse therapy and then 40 mg per day of prednisone orally, the auricular swelling lessened and the psychiatric problems improved enough for the patient to communicate verbally. However, after 2 months, recent memory storage and orientation were still impaired and MRI showed bilateral cortical atrophy within the frontotemporal lobes.

Both patients had auricular chondritis, ocular inflammation, and non-erosive polyarthritis, thus meeting the criteria for a diagnosis of relapsing polycondritis.¹ In addition, the clinical manifestations, radiological findings, and absence of HSV infections indicated non-herpetic limbic encephalitis. Despite intensive investigation, no evidence of a neoplasm or a known autoimmune disease was found.

Several previous case reports of relapsing polycondritis include confusion, disorientation, and psychiatric symptoms with or without neurological abnormalities,²⁻⁵ suggesting that limbic system involvement might be more common in this disorder than is generally thought. Histopathological evidence is limited. Although extensive cerebral and systemic vasculitis has been demonstrated on autopsy,² an inflammatory cell component has not been demonstrated.

In our patients, simultaneous brain and auricular biopsies showed active inflammation with chondritis and meningoencephalitis. The inflammatory cell components consistent with meningoencephalitis were predominantly T cells. Although our observations of perivascular cuffing with increased thickness and partial destruction of the vascular wall were consistent with vasculitis, the histopathological features were not specific for vasculitis.

Our patients responded dramatically to early treatment with high dose intravenous corticosteroids followed by an oral corticosteroid, although mild amnesia with confabulation remained in both cases. The atrophy of the medial temporal lobe and dilatation of the temporal horns of the lateral ventricle seen on MRI after treatment indicated irreversible ischaemic damage. Although we cannot exclude the possibility that the brain atrophy in the medial temporal regions resulted from the corticosteroid therapy, bilaterally reduced blood flow was seen on SPECT images of the temporal lobes (data not shown), suggesting that the atrophy was not caused by corticosteroid treatment.

Although relapsing polychondritis is a rare disorder, it should be considered in the differential diagnosis of neurological complications such as limbic encephalitis, and it is worth noting that steroid therapy may be beneficial.

F Fujiki, Y Tsuboi, K Hashimoto, M Nakajima, T Yamada

The Fifth Department of Internal Medicine, School of Medicine, Fukuoka University, Fukuoka, Japan

Correspondence to: Dr T Yamada, Fifth Department of Internal Medicine, School of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan; tyamada@fukuoka-u.ac.jp

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Diffusion tensor MRI of the cervical cord in a patient with syringomyelia and multiple sclerosis

Diffusion tensor magnetic resonance imaging (DT-MRI) is a powerful technique which provides quantitative information about structural and orientational features of the central nervous system. Development of DT-MRI based technology for identification for individual fibre tracts is important; this will allow detailed assessment of the damage to the intrinsic nerve tract, which could be helpful in understanding how tissue damage causes clinical deficits in various neurological conditions. In this context, the assessment of cord damage with DT-MRI is particularly appealing. The cord contains uniformly orientated fibres, thus obviating some caveats of anisotropy measures in the brain—for example, those related to the presence of crossing fibres on a voxel scale. Unfortunately, because of the small size of the cord and its sensitivity to artefacts related to the cerebrospinal fluid, cardiac and respiratory motions, spinal cord DT-MRI presents some technical difficulties and has been used in only very small and preliminary studies.^{1,2}

Against this background, we carried out DT-MRI of the cervical cord in a 62 year old man with syringomyelia and primary progressive multiple sclerosis. In 1989, he had complained of bilateral arm weakness and sensory loss and cervical syringomyelia was diagnosed. In 1995, he complained of progressive gait disturbances, followed by subacute onset of bilateral visual loss. Primary progressive MS was diagnosed based upon brain MRI and cerebrospinal fluid findings.³ Although he now requires bilateral assistance

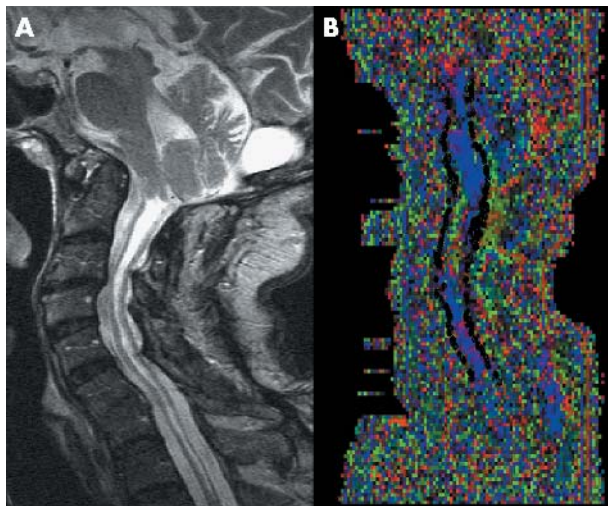


Figure 1 (A) Sagittal T2-weighted image of the cervical cord showing a syrinx extending its whole length down to the thoracic tract. (B) Sagittal SENSE single shot EPI image of the cervical cord showing preserved white matter fibre tracts around and beyond the syrinx.

for walking, following surgical intervention the upper limb signs and symptoms related to syringomyelia did not worsen over the past five years.

We acquired sensitivity encoding (SENSE) single shot echo planar imaging (EPI) sequence⁴ of the cervical cord and the brainstem of the patient. This sequence collected 16 images per section, including two images with no diffusion weighting ($b=0$ s/mm²) and 14 images with the same b factor of 900 s/mm² but with gradients applied in different directions. The diffusion unweighted images were needed to compute the DT, and the gradient orientation was chosen according to the algorithm proposed by Jones *et al.*,⁵ designed to optimise DT-MRI acquisition. The measurement was repeated four times to improve the signal to noise ratio. Three saturation bands were used, positioned in the anterior part of the neck and transversely at the edges of the field of view in the vertical direction. From the SENSE single shot EPI images, a colour encoded sagittal image was obtained. The blue colour indicates preferential fibre direction along the z axis, the green colour preferential water molecular motion along the x axis, and the red colour preferential water molecular motion along the y axis. A sagittal T2-weighted sequence of the cervical cord was also acquired.

The sagittal T2-weighted image (fig 1A) shows a syrinx extending for the whole length of the cervical cord. The colour encoded SENSE single shot EPI image (fig 1B) demonstrates the presence of preserved white matter fibre tracts around and beyond the syrinx. This latter finding is consistent with the relatively preserved motor and sensory functions of the patient, despite the extensive cervical syrinx visible on the T2-weighted image.

In this patient, the preserved tissue geometry of the cervical cord around the syrinx underpins the potential of DT-MRI to provide a more complete picture of cord damage in different neurological disorders. Compared with conventional MRI, it enabled us to obtain quantitative information of the pathological characteristics of the tissue beyond the

abnormalities visible on MRI. This shows promise in overcoming the well known discrepancy between aspects of conventional MRI and the clinical findings, reported in numerous neurological conditions. Moreover, clinical application of cord DT-MRI tractography may have prognostic value with regard to functional recovery after acute inflammatory or demyelinating pathologies, as it may enable us to investigate the residual integrity of clinically important pathways.

F Agosta, M Rovaris, B Benedetti, P Valsasina, M Filippi

Neuroimaging Research Unit, Scientific Institute and University Ospedale San Raffaele, Milan, Italy

F Agosta, M Rovaris, B Benedetti, G Comi, M Filippi

Department of Neurology, Scientific Institute and University Ospedale San Raffaele, Milan, Italy

Correspondence to: Dr M Filippi, Neuroimaging Research Unit, Department of Neurology, Scientific Institute and University Ospedale San Raffaele, Via Olgettina, 60, 20132 Milan, Italy; m.filippi@hsr.it

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Ipsilateral axial lateropulsion as an initial symptom of vertebral artery occlusion

Case reports

A 58 year old man noticed an unsteady gait when he woke up. He was unable to keep standing and fell several times to the left. On the next day, he visited our clinic. He denied vertigo, diplopia, hiccup, dysphagia, speech disturbance, numbness, and muscle weakness. On admission, ocular movements were normal in all directions. Spontaneous or gaze evoked nystagmus was undetectable with or without Frenzel's glasses. He had no skew deviation, ocular lateropulsion, saccadic pursuit, ocular dysmetria, or Horner's syndrome. Elevation of the soft palate was intact on phonation. There was no nasal voice, hoarseness, or dysarthria. The tongue did not deviate on protrusion. Other cranial nerve functions were intact. He had no weakness. Coordination of the extremities was intact. He was unable to keep standing without assistance due to marked lateropulsion to the left. Deep tendon reflexes were normal. He had no pathological reflexes. Facial sensation was intact, and so were light touch and pinprick sense in the trunk and upper limbs. Position sense was intact in the lower limbs.

Magnetic resonance imaging (MRI) showed an acute infarct in the left lateral medulla (fig 1A) and a flow signal abnormality in the left VA. Magnetic resonance angiography (MRA) confirmed an occlusion of the left VA (fig 1B). The patient was treated with intravenous argatroban, a thrombin inhibitor. On day 5, he started to improve. However, he noticed that he was unable to differentiate between cold and warm water with his right lower leg and foot while bathing. Re-examination demonstrated thermal and pain sensory loss in his right lower leg and foot. Posturographic data demonstrated abnormal body sway from left forward to right backward. He was discharged on day 10 with only slight unsteadiness.

A 55 year old man noticed a strong tendency to fall to the right on attempting to stand or walk. A few days after the onset, he noticed that he was unable to perceive coldness in his left buttock and thigh while sitting on a toilet. He did not have headache, vertigo, hiccup, dysphagia, hoarseness, numbness, or weakness. He visited our clinic on day 6. He had no Horner's syndrome, skew deviation, ocular lateropulsion, ophthalmoplegia, dysarthria, bulbar palsy, muscle weakness, or limb ataxia. He did not have spontaneous or gaze evoked nystagmus with or without Frenzel's glasses. He fell to the right on attempts to stand with his eyes closed. Deep tendon reflexes were unremarkable and pathological reflexes were negative. Sensation for light touch and position was intact. Pain and thermal sense was impaired in his left buttock and lower limb. MRI failed to show lesions in the brainstem or cerebellum. MRA demonstrated an occlusion of the right VA. He was treated with 100 mg of aspirin. Over 4 weeks, axial lateropulsion subsided, while the sensory impairment persisted.

Discussion

Isolated axial lateropulsion occurs with ischemic lesions in the inferior portion of

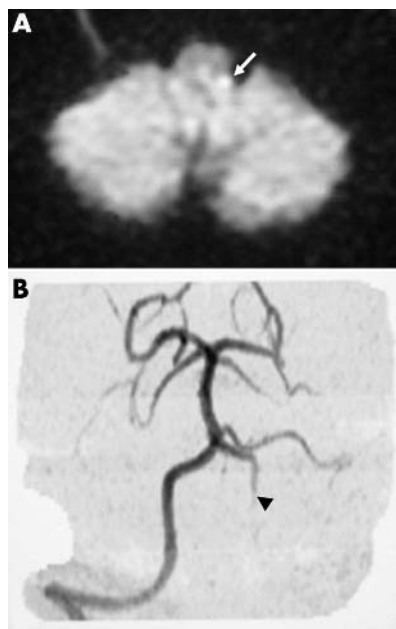


Figure 1 Diffusion weighted axial MRI (A) shows an acute infarct in the left lateral medulla (arrow). MRA (B) shows an occlusion in the distal portion of the left vertebral artery (arrowhead).

the cerebellum and tonsil¹ and with a demyelinating lesion of the superior and inferior cerebellar peduncles.² Lee *et al.* reported a patient with lateral medullary infarction who showed a gaze evoked horizontal nystagmus as well as axial lateropulsion.³ Thus, the critical structure for lateropulsion remains to be elucidated.

The patients described here did have pain and thermal sensory impairment in the contralateral lower limb, which is attributed to a lesion in the ventrolateral part of the spinothalamic tract. A very small lesion located superficially in the lateral medulla causes an atypical spinothalamic sensory deficit, which in some cases appears a few days after the onset of other symptoms.⁴ In the present cases, however, it is likely that the pain and thermal sensory deficit was present initially but was not noticed. An occlusion of the VA may have caused ischaemia in the territory of the short circumferential medullary artery directly arising from the distal VA. Structures located dorsal to the spinothalamic tract, including the spinal trigeminal tract and nucleus, and the ambiguus and vestibular nuclei were probably spared, because these patients did not have facial sensory impairment, pharyngeal or laryngeal palsy, or nystagmus. Conversely, it is highly likely that the vestibulospinal tract was involved, because it is located just ventromedial to the spinothalamic tract in the medulla. The vestibulospinal tract is considered to play an important role in the maintenance of posture by exerting strong excitatory influences on extensor muscles and inhibitory influences on flexor muscles.⁵ Thus, interruption of the vestibulospinal tract decreases extensor muscle tone of the trunk and lower limb on the side of the lesion, which is likely to cause ipsilateral axial lateropulsion. The anterior spinocerebellar tract was likely to be

involved, because it is located just dorsolateral to the spinothalamic tract in the medulla. It is possible that axial lateropulsion is associated with a lesion of the spinocerebellar tract. In the case reported by Bertholon *et al.*,² axial lateropulsion may have been caused by ipsilateral lesions of the anterior and posterior spinocerebellar tracts, which are incorporated in the superior and inferior cerebellar peduncles. Given that the vestibulospinal and spinocerebellar tracts have no projections to the ocular motor system, it is natural that these two patients did not have nystagmus or oculomotor disorders. The present findings raise the possibility that axial lateropulsion in the Wallenberg syndrome is attributable to lesions of the vestibulospinal and spinocerebellar tracts as well as central vestibular pathways.

M Arai

Department of Neurology, Seirei Mikatahara General Hospital, Hamamatsu, Japan

Correspondence to: Motomi Arai, Department of Neurology, Seirei Mikatahara General Hospital, Mikatahara-cho 3453, Hamamatsu, Shizuoka 433-8558, Japan; arai-m@sis.seirei.or.jp

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Epilepsy in one family with parietal foramina: an incidental finding?

Parietal foramina (PFM) are defects of the human skull vault, characterised by symmetrical, oval defects in the parietal bone situated on each side of the sagittal suture and separated from each other by a narrow bridge of bone. Size decreases with age and an intrafamilial variability is seen (OMIM 168500). It is thought to be a normal variant of skull development and, consequently, a benign entity.¹ Currently, loss of function mutations in two genes encoding homeobox containing transcription factors, MSX2 and ALX4, have been detected in patients with PFM.^{2,3} Parietal foramina is classified as type I, caused by MSX2 mutations, and type II, which is caused by ALX4 mutations.

Herein, we report a family with PFM type II in which two members had epilepsy and discuss the importance of neuroimaging findings to determine its possible cause. In addition, we study the variations of clinical expression, with regard to the severity of the epilepsy, in different generations.

The first patient, a boy, was referred at the age of 3 months because of a large bone defect (PFM) identified on physical examination. The mother (22 years old), aunt (25 years old), and grandfather (55 years old) also had PFM, but smaller than the child's, showing an age related size variation. Molecular analysis, reported elsewhere,⁴ showed that this family had an ALX4 mutation (PFM type II). History, neurological examination, and neuroimaging evaluations were obtained from three relatives. The aunt refused further analysis. Electroclinical investigation consisted of a detailed clinical history, review of charts, and video electroencephalogram (V-EEG) monitoring. Neuroimaging evaluation consisted of helical computed tomography scans of the head (with post-processing three dimensional views of the cranial vault), 1.5T magnetic resonance imaging (MRI) at three orthogonal planes with conventional SE (before and after intravenous paramagnetic contrast administration), and magnetic resonance venography.

At the age of 4 years, the patient was referred to our laboratory for elucidation of paroxysmal events, described as brief periods of "blindness". He was born at term, by caesarian section after an uneventful pregnancy. During follow up, physical and neurological examinations revealed normal neurological development and physical growth. Seizure semiology was highly suggestive of an occipital origin; seizures were characterised by visual phenomena (black-outs), progressing to loss of contact and forced eye and head deviation to the left, followed by vomiting and headache. Onset occurred during infancy, at 8 months, and up to the latest evaluation, a total of six seizures had occurred. Carbamazepine was replaced by valproate in an attempt to improve seizure control.

The mother had a history of epilepsy with the same characteristics as those seen in the child, although the seizures were shorter. Onset occurred later, during puberty, at 15 years. She had four stereotyped seizures, controlled with phenobarbital (50 mg/day), which was taken for two years. Her past and current medical history was normal, including neurological examination.

Electroencephalographic tracings showed frequent, sharp waves over the left posterior quadrant in the child (fig 1A). Although V-EEG was done, we did not register his seizures because of their sporadic nature. The mother had a normal current EEG, but previous EEG reports described the same abnormality as in her child.

The grandfather had no current neurological or cognitive deficits. He denied a history of seizures, syncope, migraine, or other paroxysmal events. His EEG was normal.

Neuroimaging investigation with 1.5T MRI showed a malformation of occipital infolding, suggestive of a polymicrogyric cortex over the posterior regions in all three patients, although this was more prominent in the child (fig 1B).

This family had the classic phenotype for PFM, in this case type II (ALX4 mutation), including age related expression with regard to the size of the foramina. In contrast to the current idea that PFM is not associated with neurological disorders, the child and his mother had epilepsy with occipital lobe seizures. Reviewing previous studies, Kyte³ described one patient with identical epilepsy and EEG features as seen in our patients, including the age related improvement. An important issue in this family, not previously reported, is the earlier onset and higher frequency of events in the child. Analysis of this family showed an intrafamilial variability, with a more severe and earlier presentation of epilepsy in the youngest member. Our findings suggest a generation related modulation of the clinical picture, which may explain why some patients may present with a clinical condition whereas others remain asymptomatic.

Our family had an ALX4 mutation, but there is no evidence of phenotype-genotype differences between patients with PFM type I (MSX2 mutation) and II (ALX4 mutation). In an experimental study, Satokata *et al* described Msx-2 mutant mice with seizures accompanied by abnormal development of the cerebellar cortex,⁶ which suggested a structural malformation as the cause of seizures, as seen in our patients. The association of cortical anomalies and epilepsy is well known and the neuroimaging study in our family showed the coexistence of a cortical malformation on the

posterior region in the three relatives with PFM, including the asymptomatic member. Reddy *et al* described cortical and vascular anomalies,⁷ corroborating that these findings may not be uncommon, and are now being identified because of advances in neuroimaging.

Malformations of cortical development are seen in some syndromes found with other diseases that have a well known genetic basis. Polymicrogyria seems to result from genetic or environmental factors, or both. In our patients, although a genetic anomaly was found, the abnormal cortex overlies vascular territories. This may seem contradictory, but it is possible that the cortical anomalies in this family are the consequence of a vascular abnormality which, in turn, could have been caused by the genetic anomaly.

In conclusion, we suggest that some cases of PFM are not as benign as thought previously. From a practical point of view, the documentation of a family with neurological symptoms because of cortical abnormalities indicates that more extensive neuroimaging is recommended for patients with PFM, in addition to the investigation of families, especially when patients are symptomatic.

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K D Valente

Laboratory of Clinical Neurophysiology, Institute and Department of Psychiatry, University of São Paulo (USP) Medical School, São Paulo 01246-903, Brazil

M Valente

Paediatric Neuroradiology Unit, Departments of Paediatrics and Radiology, University of São Paulo (USP) Medical School

Correspondence to: Dr K D Valente, Rua Jesuino Arruda, 901, São Paulo 01246-903, SP, Brazil, CEP:04532-082; kettevalente@msn.com/kvalente@usp.br

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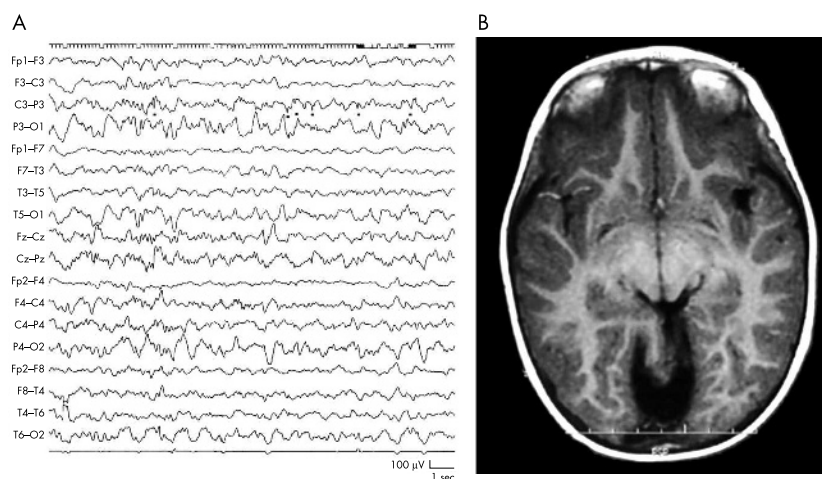


Figure 1 The 4 year old boy. (A) Electroencephalogram, during sleep, shows low amplitude sharp waves over posterior regions, more prominent on the left parietal region. (B) Axial plane magnetic resonance imaging without contrast enhancement (T1) shows an unusual pattern of cortical gyration with polymicrogyria over bilateral occipital regions.

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Baroreflex failure secondary to paraneoplastic encephalomyelitis in a 17 year old woman with neuroblastoma

Baroreflex failure is a rare cause of postural hypotension but should be considered in any patient with a diffuse central nervous system disease involving the brainstem. Paraneoplastic encephalomyelitis (PEM) is such a disease and, although rare, is becoming more frequently diagnosed because of improved imaging and specific antibody testing. We present the first case of baroreflex failure secondary to PEM. In January 2002, a 17 year old woman presented with a 3 week history of pain in the right shoulder which spread down the forearm to the radial border of her hand. She had also become anorexic and lost 18 kg over 3 months. A mild resting tachycardia was noted but there were no objective neurological signs, and routine blood tests, including inflammatory markers, were normal. In March, both pupils became dilated, non-reactive to light or near stimuli, and myotonic (that is, Holmes-Adie pupils). Limb reflexes were decreased and nerve conduction studies demonstrated a mild motor-sensory polyneuropathy. The aetiology of her anorexia was thought to be psychological and over the next 3 months she was treated with sedatives, antidepressants, and motility agents. She regained 12 kg but her neurological abnormalities persisted, and she developed psychomotor retardation and symptomatic postural hypotension. In July she underwent tilt testing and autonomic studies.

The patient was positioned horizontally on the tilt table and continuous blood pressure (BP) was monitored using digital plethysmography, stroke volume was derived from the arterial pulse wave, heart rate (HR) from the ECG, and muscle sympathetic nerve activity (MSNA) from the right peroneal nerve using the microneurographic technique.¹ All measurements were averaged over 1 min intervals. Recordings were made during "ice to face" stimulation and 60° head up tilt (fig 1). The results, with normal values from our laboratory in brackets, were as follows: resting horizontal, mean BP was 102 mm Hg (mean (SE): 111 (3) mm Hg), HR 110 bpm (75 (4) bpm), and MSNA 84 bursts/min (31 (4) bursts/min).² After 2 min of 60° head up tilt, mean BP was 46 mm Hg (111 (5) mm Hg), HR 125 bpm (81 (3) bpm), and MSNA 64 bursts/min (44 (5) bursts/min), and cardiac output was decreased by 50% (normal response is a 20% decrease from 3.2 (2) to 2.5 (0.3) l/min/m²). Resting horizontal, venous noradrenaline was in the high normal range at 3100 (470–3800 pmol/l) and during tilt, arginine vasopressin (AVP) levels increased from 6.1 to 7.3 pmol/l, much less than expected for the degree of hypotension. During ice to face stimulation, mean BP, HR, and MSNA levels increased to 114 mm Hg, 118 bpm, and 120 bursts/min, respectively.

Magnetic resonance scanning of the brain and spine were normal. Screening for common causes of neuropathy was negative. A radionuclide study demonstrated delayed gastric emptying. Paraneoplastic autoantibody testing was positive for immunofluorescent anti-neuronal nuclear antibody type 1 (ANNA-1, also known as "anti-Hu" titre 1:30 720), confirmed by western blot against native neuronal antigen. In October 2002 a

mass was found in her right neck and biopsy demonstrated a neuroblastoma. Further bone scanning and bone marrow biopsies demonstrated no evidence of metastatic disease. She was treated with chemotherapy followed by surgery and local radiotherapy. Repeat scanning demonstrated complete remission. Her gastrointestinal symptoms improved, and the postural hypotension, pupillary signs, and psychomotor retardation remained stable.

In retrospect, all the clinical findings are consistent with PEM, consisting of: (a) limbic encephalitis causing psychomotor retardation, (b) sensory neuropathy affecting the limbs, (c) autonomic dysfunction including Holmes-Adie pupils and impaired baroreflex modulation of heart rate and vasoconstriction, and (d) enteric neuropathy causing gastrointestinal dysmotility.³ As we have demonstrated, the diagnosis may be difficult. This is primarily because paraneoplastic syndromes are rare (the incidence is less

than 0.1% in cancer patients), neurological symptoms usually predate the discovery of the tumour, and the antibody tests are not widely available.³ Psychomotor retardation and anorexia were initially thought to be secondary to a psychological disorder, despite the neurological findings and the demonstration of delayed gastric emptying. The tilt test results indicated a polyneuropathy as the primary cause of the patient's symptoms. Following exclusion of common neuropathic aetiologies, the diagnosis of PEM was made following the finding of high titre ANNA-1 antibody and the neuroblastoma. The antibody recognises a family of RNA binding proteins (35–40 kDa) in neurones and certain tumours including small cell lung carcinoma and neuroblastoma which share a common ectodermal origin.³ The nuclear antigens are expressed by all small cell lung carcinomas and most neuroblastomas although the antibody is not usually present.

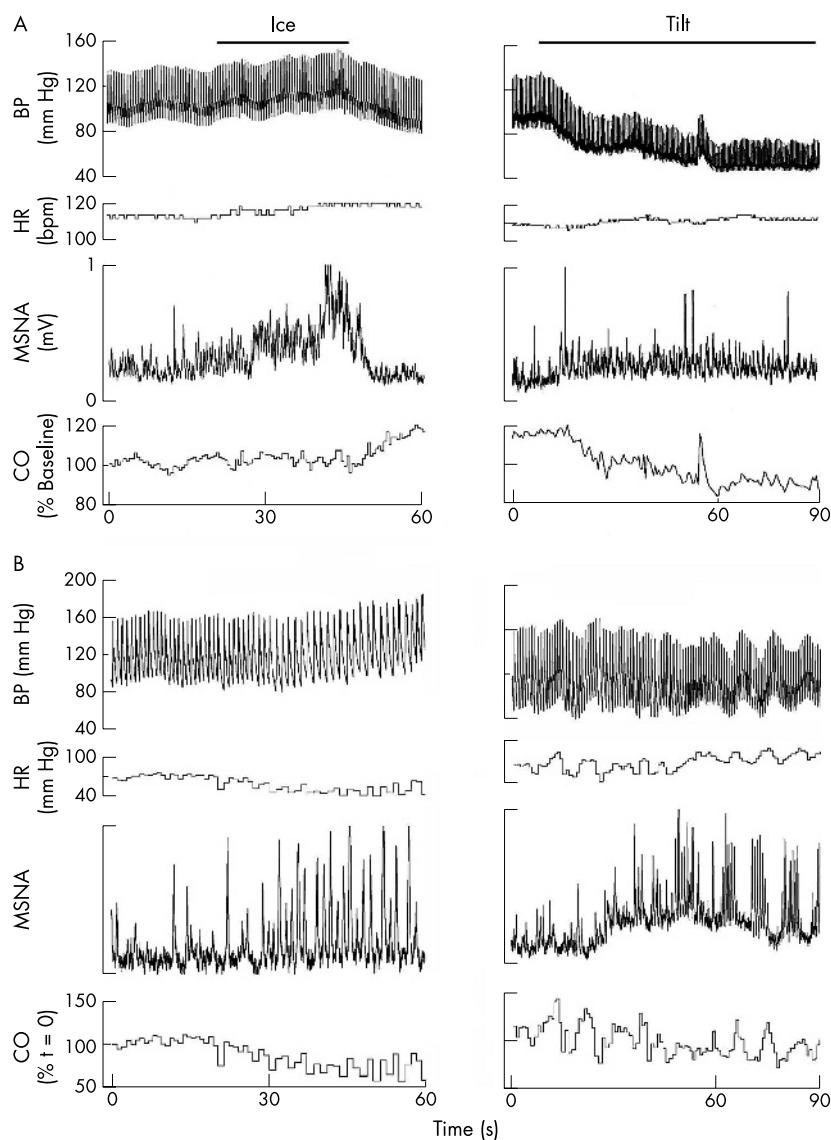


Figure 1 (A) Recordings from the patient during the application of ice to the face (the diving reflex) showing a normal increase in blood pressure (BP), heart rate (HR), and muscle sympathetic nerve activity (MSNA), while cardiac output (CO) is maintained. However during head up tilt, there is an inappropriate fall in BP with no increase in MSNA. The fall in CO is exaggerated. (B) Recordings from a normal patient of similar age show similar responses to ice, but during tilt, BP is maintained, MSNA increases, and CO decay is less.

Most paraneoplastic syndromes associated with neuroblastoma have been reported in young children with cerebellar ataxia, myoclonus, and opsoclonus. ANNA-1 antibodies are usually present in patients with small cell carcinomas and paraneoplastic gastroparesis but have not been previously reported in association with neuroblastoma and autonomic dysfunction.^{3,4} Although new antibodies continue to be reported in association with paraneoplastic neurological disorders, the majority of patients with subacute onset of autonomic failure or gastrointestinal dysmotility are considered idiopathic. The most specific marker autoantibody recognised so far is directed at postsynaptic acetylcholine receptors in autonomic ganglia, and was not detected in our patient.⁴

We suspect that the primary mechanism for her severe postural hypotension was baroreflex failure resulting in increased, rather than decreased, basal efferent sympathetic activity. Baroreflex failure refers to loss of inhibitory feedback from the arterial baroreceptors to the brainstem. The baroreflexes are the most important mechanism for maintaining blood pressure during rapid changes in posture and central blood volume. Baroafferents may be damaged in the periphery (for example, arterial baroreceptors during carotid endarterectomy) or, as we suspect in this patient, the central nervous system where they enter the superior medulla.⁵ We hypothesise that baroreflex failure caused severe postural hypotension by two mechanisms: firstly, the immediate vasoconstrictor and AYP responses to changes in central blood volume were decreased; and secondly, increased sympathetic activity at rest mediated chronic splanchnic vasoconstriction and decreased venous capacitance. This caused decreased venous return and an exaggerated fall in cardiac output in response to upright posture. Efferent sympathetic failure was unlikely because MSNA activity was increased at rest and increased normally (with resulting hypertension) during the diving reflex. The diving reflex is mediated by increased sympathetic output from the medulla in response to trigeminal sensory (as opposed to baroafferent) pathways.

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D L Jardine

Department of General Medicine, Christchurch Hospital, Christchurch, New Zealand

C P T Krediet

Academic Medical Center, Amsterdam, The Netherlands

B A Robinson

Department of Oncology, Christchurch Hospital, Christchurch, New Zealand

Correspondence to: D L Jardine, General Medicine Department, Private Bag 4710, Christchurch Hospital, Christchurch, New Zealand; david.jardine@cdhb.govt.nz

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Acquired ocular motor apraxia from bilateral frontoparietal infarcts associated with Takayasu arteritis

The relatively rare syndrome of acquired ocular motor apraxia is characterised by difficulty in initiating saccades to command and to visual targets, usually in all directions.¹

Case report

Our patient was a 52 year old left handed and non-literate man. He was admitted to a local hospital with the complaint of acute and persistent thoracic and epigastric pain radiating to his back. Five days later he developed acute loss of consciousness and was sent to our hospital.

Blood pressure was 170/100 mm Hg from the right arm and 160/100 mm Hg from the left, the right femoral artery was pulseless, and the epigastrium was painful on palpation. He was stuporose, disoriented, and his cooperation was limited to simple commands only. He had bilateral ptosis with his eyes fixed in the primary position. Convergence was absent. However, an oculocephalic reflex could be elicited in both vertical and horizontal directions. His left nasolabial sulcus was somewhat reduced. He had paresis of both his arms and his left leg, while the motor strength in his right leg was almost completely normal. Hoffman and Babinski signs were positive on the left side, with hyperreflexia. The tendon reflexes were normal on the right side and no pathological reflexes were elicited. He had urinary incontinence.

On the third day of admission he appeared apathetic. Although his thinking was slowed, and his affect was flattened, he could answer simple questions and obey simple commands. He still had difficulty in understanding complex orders. His ptosis had resolved but the hypertonia in the left upper extremity was more pronounced. His eyes were still fixed in the primary position.

In the following few days, when he was no longer stuporose, he was observed to execute spontaneous eye movements in all directions without associated head movements, but he was unable to carry out any eye movements when he was instructed to gaze at an object. He was also unable to execute pursuit movements, and there was no optokinetic nystagmus response. On bedside examination, optokinetic nystagmus was tested for by rotating a drum vertically and horizontally before his eyes. Foveal smooth pursuit was tested by asking the patient to follow the

movement of a target light produced by a light source. Examination of the visual fields with confrontation was normal. He also had no visual extinction. Two months after admission, the patient was transferred to a rehabilitation centre, showing full cooperation and orientation and with his eye movements partly recovered. He had no anosognosia or right-left disorientation. His muscle strength had only mildly improved and he had severe hypertonia in his paretic extremities, with clonus of the left leg. A month later he was discharged from the rehabilitation centre without any eye movement abnormality. The oculocephalic reflexes were spared throughout the course of the illness.

Blood studies showed a leucocytosis (14 600 WBC/mm³) and an inflammatory reaction (erythrocyte sedimentation rate 124 mm/h, C reactive protein 110 mg/l). Cranial computed tomography (CT) showed hypodense lesions of cortical grey matter at the level of both cerebral convexities. Cranial magnetic resonance imaging (MRI) showed subacute infarcts involving the cortical grey matter of both frontal and parietal border zone areas bilaterally. The frontal eye field (FEF, at the intersection of the precentral sulcus and the superior frontal sulcus) and the parietal eye field (PEF, in the posterior part of the intraparietal sulcus) were involved bilaterally (fig 1A), whereas both supplementary eye fields (SEF, in the medial wall of the superior frontal gyrus) were spared (fig 1A). Coronal section through the parietal lobe revealed that the intraparietal sulcus (PEF) was involved, whereas the posterior cingulate cortex (PCC) was spared (fig 1B). Three dimensional time of flight magnetic resonance angiography (MRA) showed no abnormality of the cerebral vessels. Contrast enhanced MRA revealed irregularity of the vessel wall beginning from the aortic arch and extending the abdominal aorta (fig 1C). Cutaneous biopsy from the abdomen supported a diagnosis of vasculitis. The patient was diagnosed as having Takayasu arteritis.

Comment

The case is a good example of "acquired" ocular motor apraxia. It appears that both frontal eye fields of the patient were affected by ischaemia. We concluded that ischaemia in the border zone areas of both hemispheres was the result of sudden haemodynamic insufficiency during dissection of the aorta.

Saccadic eye movements can be divided into three types: reflexive, intentional, and spontaneous saccades. Reflexive saccades are triggered by the sudden appearance of an external visual stimulus, whereas intentional and spontaneous saccades are internally triggered. Three cortical areas may trigger saccades—the frontal eye field (FEF), the supplementary eye field (SEF), and the parietal eye field (PEF). The FEF are involved mainly in intentional visual exploration (intentional saccades), the PEF mainly in reflexive visual exploration (reflexive saccades), and the SEF mainly in the preparation of motor programmes. SEF also appear to control spontaneous saccades.²

Only bilateral lesions affecting these areas result in visible saccade disturbances on bedside examination. Saccadic eye movement disorders resulting from unilateral lesions of these areas can only be revealed by electro-oculographic recordings.³ Acquired ocular motor apraxia is usually caused by

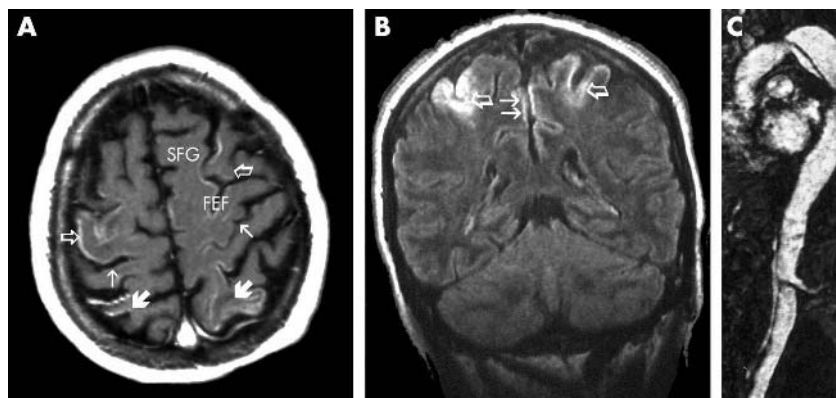


Figure 1 (A) Axial contrast enhanced T1 weighted magnetic resonance scan showing gyriform cortical enhancement caused by laminar cortical necrosis following a hypoxic ischaemic episode. Neural parenchyma of both the precentral area (frontal lobe, open arrow) and the postcentral area (parietal lobe, thick arrow) was involved. The thin arrow indicates the central sulcus. FEF, frontal eye field; SFG, superior frontal gyrus. (B) Contrast enhanced coronal section through the parietal lobe. The intraparietal sulcus (PEF, open arrows) was involved as well as the medial part of the parietal lobe (thin arrows), while posterior cingulate cortex was spared. (C) Contrast enhanced magnetic resonance angiography showing irregularity of the vessel wall beginning from the aortic arch and extending to the abdominal aorta.

bihemispheric infarcts.¹ Our patient could not be evaluated for any apraxia of his extremities or for optic ataxia because of the degree of paresis in both his arms. He might also have had an optical ataxia during the period when he had anosognosia and right–left disorientation. The development of a substantial degree of paresis with hypertonia in the first days of the ischaemic insult, and the continuation of these symptoms after ocular motor apraxia had resolved, may suggest that the anterior border zone areas were affected to a greater degree than the posterior border zone areas.

For this reason the functions of both the FEFs might have been undertaken by the PEFs. It seems likely that this role could be assumed by other areas, such as the posterior areas, as an adaptive response after injury.⁴ Bilateral damage to the PEFs may result in severe impairment of pursuit movements.¹ The posterior cingulate cortex (PCC)—which is known to show neuronal activity during pursuit movements²—was spared in our patient. However, the medial superior temporal lobe (MST), located close to the intraparietal sulcus, was possibly damaged. This area is known to be implicated in pursuit

eye movements from single cell recording studies in the monkey.³

We observed in our patient that ocular apraxia and pursuit movements of the eyes began to resolve simultaneously. This observation may suggest that recovery in the PEFs might have occurred first and have compensated for the FEFs. Recovery of spontaneous saccades in the first few days of ischaemia might indicate that the SEFs, which are assumed to be responsible for these eye movements, were not seriously damaged.

B O Genç, E Genç, L Açıık, S İlhan

Selçuk University, Meram Medical Faculty,
Department of Neurology, Konya, Turkey

Y Paksoy

ULTRA Görüntüleme Merkezi (Imaging Centre), Konya

Correspondence to: Dr Bülent Oğuz Genç, Selçuk University, Meram Medical Faculty, Department of Neurology, Konya 42080, Turkey; bogenc@mynet.com

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PostScript

LETTERS

Delayed early morning turn "ON" in response to a single dose of levodopa in advanced Parkinson's disease: pharmacokinetics should be considered

The pathophysiology underlying the fluctuations in response following oral levodopa therapy is complex and includes peripheral and central factors. The short half-life of levodopa, erratic gastrointestinal absorption, and competitive transport across the blood-brain barrier have been regarded as factors responsible for the fluctuating plasma and striatal concentrations of levodopa. Indeed, failure of an oral dose to produce an effect or delay in the onset of action have been associated with problems in absorption.^{1,2}

We studied the pharmacokinetics of levodopa in 19 patients with advanced Parkinson's disease (12 men, seven women; period of evolution of illness more than 10 years) with and without a delayed response to the first drug dose in the morning (delayed early morning turn "ON"). The patients were selected according to the UK Brain Bank criteria; those who could not tolerate an assessment after 12 hours without taking their antiparkinsonian medication were excluded. All patients signed an informed consent form before being included in the study.

Medication and food were withheld after midnight the night before the study day. All patients' regular therapeutic first (morning) levodopa/carbidopa dose was between 125 mg and 250 mg. Therefore all patients received a single oral dose of levodopa/carbidopa (250/25 mg) at 9:00 am, to ensure that all had a response. A low protein breakfast was served three hours after drug administration.

Blood samples were collected every 20-30 minutes for six hours following drug administration. Plasma levodopa concentration was determined using high performance liquid chromatography (HPLC) with electrochemical detection as previously described.³ Peak plasma concentration (C_{max}), the time elapsed to reach the C_{max} , area under the curve, half-life, clearance, and slope in the absorption phase (K_{abs}) were determined using PK Solutions version 2 software (Summit, USA <http://www.summitpk.com/>). Motor performance was evaluated using a tapping test on the more affected side. In this test, patients are requested to alternately tap two points separated by a distance of 30 cm with the fingers of the hand (of the most affected side) for one minute. In the present study, total tapping—that is, the number of times the patient is able to carry out the task, was recorded every 20 minutes during the first two hours and then every 30 minutes until the completion of the test. The Unified Parkinson's Disease Rating Scale for motor examination (UPDRS-III) was applied prior to (baseline) and at the time of the "best on" after levodopa administration. Delayed early

morning turn "ON" was defined as the condition in which the effect of levodopa in the tapping test (a 50% basal score improvement; maximal levodopa effect = 100%) appeared more than 40 minutes after the administration of the drug.

For all patients, the results are given as mean (SD) and Student's *t* test ($p < 0.05$) was used to determine the significance between the differences.

The UPDRS-III and tapping tests were used to verify the occurrence of the drug effect, thus allowing patients with and without delayed early morning turn "ON" to be distinguished. In clinical practice, a standard dose of levodopa becomes effective within the first 20 minutes after drug administration. For separating the patients without and with delayed early morning turn "ON", the latter were considered as those in whom a standard levodopa dose took more than 40 minutes to become effective. These patients showed a tendency to have worse baseline and best ON scores than the patients without delayed early morning turn "ON", although this trend was not statistically significant.

As shown in fig 1, a significant difference was found between the C_{max} values of patients without delayed early morning turn "ON" (mean 3552 (SD 1208) ng/ml) and those of patients with delayed response (1146 (289) ng/ml). None of the other pharmacokinetic parameters showed statistically significant differences.

To obtain an adequate response in Parkinson's disease the appropriate oral dose of levodopa is usually determined bearing in mind that worse symptoms may be treated with higher drug dosages or more frequent doses as long as side effects do not appear. This simplistic approach does not take into account the evolution of the disease, in which not only do the symptoms become more evident but also the treatment progressively

loses its effectiveness. Indeed, patients with Parkinson's disease, whose illness has evolved over several years and evidence motor fluctuations tend to show a delayed response to the first oral levodopa dose compared with patients with non-fluctuating motor symptoms. The mechanism of this phenomenon is still poorly understood.⁴ In the present study, patients with delayed early morning turn "ON" had significantly lowered C_{max} values. Even though we are unable to give a direct explanation for the molecular events underlying this finding, it is clear from our data that the pharmacokinetics of levodopa play an important role in the occurrence of delayed early morning turn "ON".

Since all other pharmacokinetic parameters (including K_{abs}) of the patients with and without delayed response showed no differences, one might consider that the rate of absorption is basically the same in both groups. In addition, it has been found that both subcutaneous administration of apomorphine⁵ and pyloric bypass with duodenal infusion of levodopa⁶ are useful because they reduce plasmatic variability and improving clinical response in patients with delayed early morning turn "ON" by increasing functional "ON" time with less dyskinesia and fluctuation. Therefore, we propose that altered gastric emptying but not the intestinal absorption rate might be linked to the delay in the clinical response observed. However, further studies are necessary to address this issue.

Slower progression of the neurodegenerative process and the loss of levodopa effect are usually associated with the degeneration of dopaminergic nerve terminals in the central nervous system (pharmacodynamic factor).⁷ The data presented here highlight the need to also consider pharmacokinetic factors when analysing the delayed early

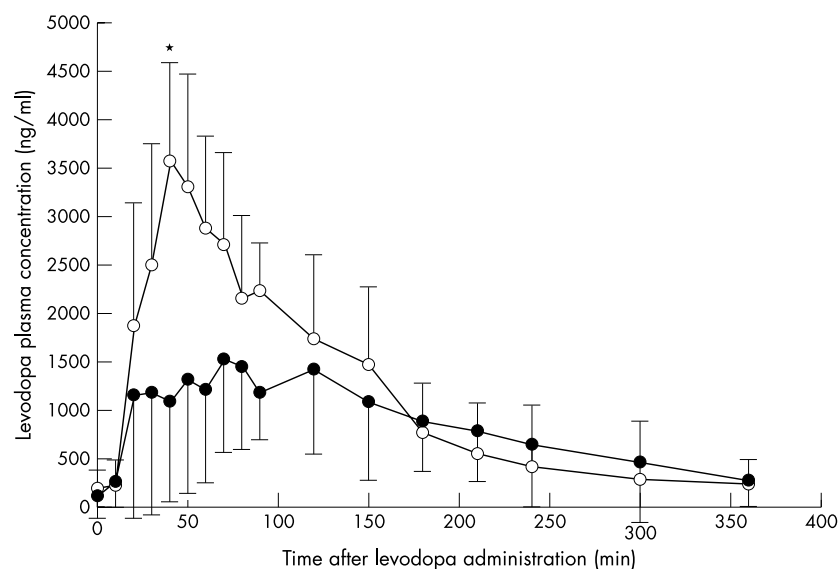


Figure 1 Pharmacokinetic curve after a single dose of levodopa. Data are shown as mean (SEM): filled circles, 12 patients with delayed early morning turn "ON"; open circles, seven patients without delayed early morning turn "ON". *, $p < 0.05$.

morning turn "ON" condition and considering the best doses and regimen of drug administration in patients with advanced Parkinson's disease.

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P Chaná, C Kuntsmann

Movement Disorders Unit, Service of Neurology and Neurosurgery, DIPRECA Hospital, Universidad de Santiago de Chile, Chile

M Reyes-Parada, P Sáez-Briones

Neurosciences Unit, Facultad de Ciencias Médicas, Universidad de Santiago de Chile, Chile

Correspondence to: Dr P Chaná, Universidad de Santiago de Chile, Belisario Prats 1597B, Santiago, Chile; pedrochana@mi.cl

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Lethal encephalopathy in a patient with isolated nervous system vasculitis

Vasculitic neuropathy can occur in patients with connective tissue diseases. On the other hand, non-systemic vasculitic neuropathy has been established as an independent clinical entity, and the risks for systemic spread and death are small.¹ In patients with this disorder, vasculitis is limited to the peripheral nervous system (PNS), and histological evaluation is essential for the definitive diagnosis. We encountered a patient with isolated nervous system vasculitis who developed lethal encephalopathy. He had a persistently high titre of anti-GM1 IgG antibody, which is occasionally detected in patients with chronic inflammatory demyelinating polyneuropathy (CIDP).

Case report

A 67 year old man had been under treatment for type 2 diabetes for 10 years. In September 1998, he was referred to our hospital because of weight loss and numbness of the lower limbs. He was mentally alert and had exophthalmos. Muscle weakness was prominent in the distal muscles of all four limbs. Sensation was disturbed with a "stocking and glove" distribution. Deep tendon reflexes were diminished in all four extremities.

Results of laboratory examination indicated diabetes mellitus and hyperthyroidism (haemoglobin A_{1c} 6.8% (normal range 4.3-5.8); thyroid stimulating hormone <0.03 µIU/ml (normal range 0.2-3.2); free triiodothyronine 13.2 pg/ml (normal range 2.9-6.0); free thyroxine 7.65 ng/dl (normal range 0.78-2.10); antithyroglobulin antibody 3200 (normal <100); antithyroid microsomal antibody 26 800 (normal <100); antithyrotropin receptor antibody 16.1% (normal

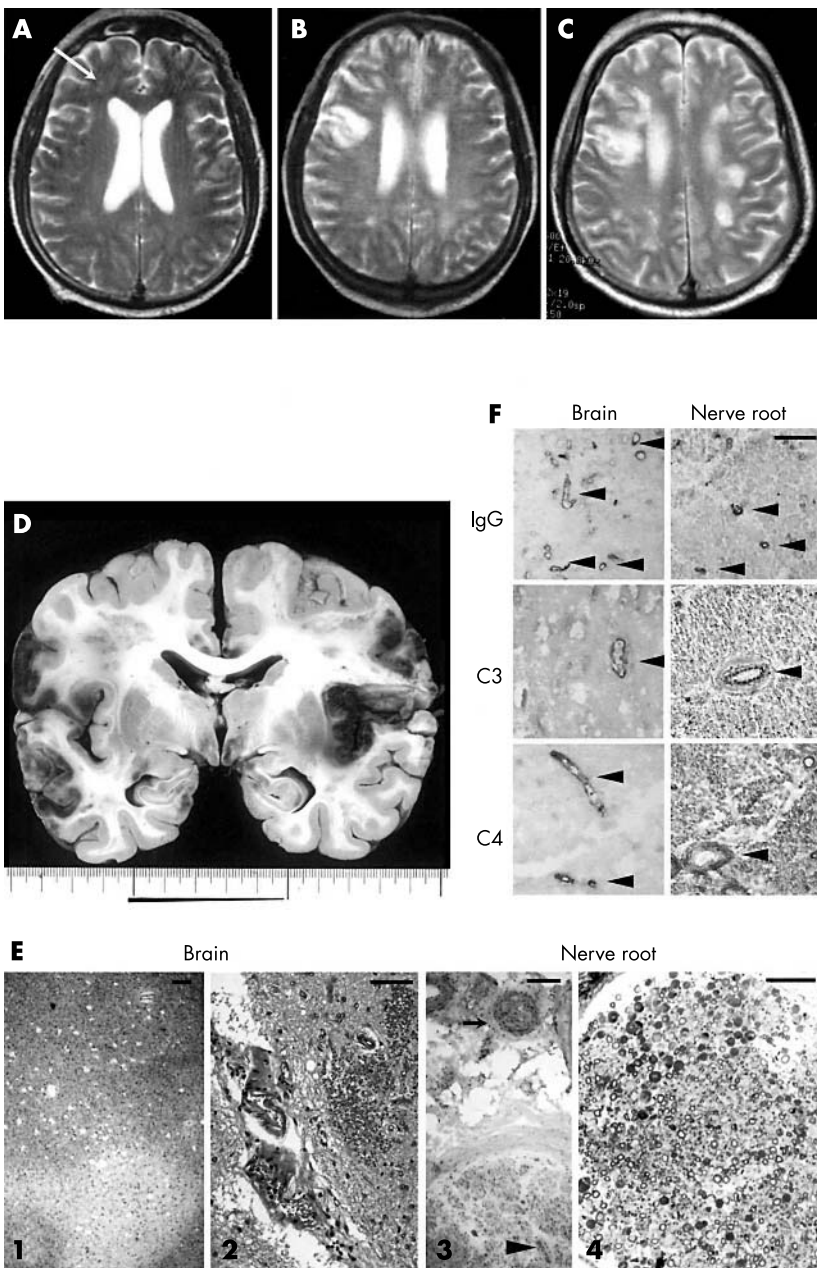


Figure 1 (A-C) Brain MRI T2-weighted images. (A) On 11 May 2000 small high intensity signals in frontal white matter (arrow) were seen. (B) On 1 June 2000, a high intensity signal appeared in the right temporal cortex. (C) On 12 July 2000, the high intensity areas were increased in number and enlarged in the cerebral cortex and white matter. (D) Coronal section of autopsied brain showed multiple plaques in white matter and multiple haemorrhagic transformations in the cortex. (E) 1—Demyelination and axonal loss in cerebral white matter (Klüver-Barrera stain); 2—haemorrhagic transformation in the temporal cortex (H&E stain); 3—vasculitic occlusion of small epineurial (arrow) and endoneurial vessel (arrowhead) in a peripheral nerve root (H&E stain); and 4—demyelination and axonal degeneration in a peripheral nerve root (toluidine blue stain). (F) Immunohistochemical staining for IgG, C3, and C4 in the temporal cortex and in a peripheral nerve root showed intense signals in the lumens of vessels. Bar, 100 µm.

<10); thyroid stimulating antibody 207% (normal <150)). Serological examination for antiganglioside antibodies revealed anti-GM1 IgG, and the titre was 25 900 (normal <800) by enzyme linked immunosorbent assay. No other antiganglioside antibodies were detected by thin layer chromatography immunoblotting. Antimyelin associated glycoprotein and antinuclear antibody were not detected. Cerebrospinal fluid (CSF) cell count was 4/mm³ and protein level was 53 mg/dl (normal <45). Oligoclonal bands and myelin basic protein were not detected.

Motor nerve conduction velocities (MCV, m/sec) and distal compound muscle action potential amplitudes (CMAP, mV) were as follows: median nerve 52.5 (normal >49) and 0.4 (normal >5); ulnar nerve 45.5 (normal >48) and 2.7 (normal >4); tibial nerve 40.0 (normal >50) and 3.8 (normal >7); peroneal nerve 36.9 (normal >48) and 1.2 (normal >3), respectively. Conduction blocks were observed bilaterally in the ulnar and peroneal nerves at the common sites of entrapment. Sensory nerve conduction velocity was 37.8 m/sec (normal >48) in the median nerve and was not evoked in the sural nerve. The patient was diagnosed as having CIDP and Graves' disease. After treatment with thiamazole, thyroid function and levels of thyroid related autoantibodies normalised but the peripheral neuropathy remained. Muscle weakness and numbness improved following treatment with prednisolone at 50 mg/day and pulse intravenous methyl prednisolone 1 g/day for three days in June 1999 but his symptoms exacerbated again after five months. Diabetes and hyperthyroidism were well controlled, but anti-GM1 IgG titre was elevated to between 11 900 and 40 700. Despite intravenous immunoglobulin (IVIg) therapy, he suddenly had convulsions and consciousness disturbance on 11 May 2000. CSF examination showed a normal cell count, but the protein level was increased to 121 mg/dl. Nerve conduction studies revealed further reduction in CMAP amplitude with conduction block and delayed MCVs. Brain magnetic resonance imaging (MRI) demonstrated slightly high intensity signals in frontal white matter on T2-weighted image (fig 1A, arrow). Intra-arterial angiography showed no evidence of a cerebrovascular accident. His consciousness disturbance responded partially to treatment with pulse methyl prednisolone, IVIg, and plasma exchange. However, a T2-weighted MRI in June 2000 showed large high intensity signals in the right frontal cortex and white matter (fig 1B). Some of the lesions were enhanced with Gd-DTPA on a T1-weighted image. In July 2000, the lesions were enlarged in the cerebral cortex and white matter (fig 1C). Despite repeated immunomodulating therapies, he died on 17 August 2000. An autopsy of the brain showed disseminated multiple plaques in the pons and bilaterally in the cerebral white matter (fig 1D), corresponding to demyelination and axonal loss (fig 1E(1)). Haemorrhagic transformations with mild infiltration of inflammatory cells in the vascular and perivascular regions were observed in the temporal cortex (fig 1E(2)) and cerebellar hemisphere. Peripheral nerve roots obtained from the lumbar plexus exhibited vasculitic occlusion of small epineurial and endoneurial vessels with inflammatory cell infiltration (fig 1E(3)) and demyelination and axonal degeneration (fig 1E(4)). Immunohistochemical study revealed intense signals for IgG, C3, and C4

in vessels from the temporal cortex, white matter, and peripheral nerve root (fig 1F), but the signals were unremarkable in specimens of unaffected regions. Vasculitis was not evident except for in the nervous system.

Discussion

The present patient showed chronic sensorimotor polyneuropathy similar to CIDP. However, the most prominent feature was lethal encephalopathy and isolated vasculitis in the nervous system. The brain lesions mainly consisted of demyelinating changes in the white matter, but the lesions in the temporal cortex and peripheral nerve roots indicated vasculitis. Immune deposits of IgG and complements were detected in the vascular regions only in the affected regions of the nervous system. The immune deposits may be associated with vascular damage resulting in cortical haemorrhagic transformation. To the best of our knowledge, this is the first report of histopathological analysis of CNS involvement in vasculitic neuropathy with no evidence of systemic collagen disease.

Anti-GM1 antibody is occasionally detected in patients with CIDP or systemic collagen disease with neurological manifestations.² However, it has not been studied in patients with non-systemic vasculitic neuropathy. Brain endothelial cells and endoneurial cells share GM1 ganglioside antigens with peripheral nerve tissues, and anti-GM1 antibody facilitates leakage in the blood-nerve barrier.³ These findings indicate that anti-GM1 antibody might have induced demyelinating change and vascular damage in both the PNS and CNS of the present patient. It is noteworthy that CNS white matter lesions have been detected in patients with CIDP.⁴ Interestingly, anti-asialo-GM1 antibody has been frequently detected in patients with Graves' disease or Hashimoto's thyroiditis.⁵ Although Graves' disease may have contributed to the development of the encephalopathy, lethal encephalopathy is an extremely unusual outcome not only in non-systemic vasculitic neuropathy but also in thyrotoxic autoimmune encephalopathy.⁶

In conclusion, vasculitic neuropathy seemed to have resulted in the development of lethal encephalopathy in the present patient. Furthermore, a common autoimmune mechanism mediated by anti-GM1 antibody similar to that in CIDP may have been involved in the lesions in the CNS as well as PNS.

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Y Sumitomo, M Kunishige

Department of Medicine and Bioregulatory Sciences, University of Tokushima Graduate School of Medicine, Tokushima, Japan

N Satake

Department of Molecular and Environmental Pathology, University of Tokushima Graduate School of Medicine, Tokushima, Japan

K Shinno

Department of Neurosurgery, University of Tokushima Graduate School of Medicine, Tokushima, Japan

M Kawashima, T Matsumoto, T Mitsui

Department of Medicine and Bioregulatory Sciences, University of Tokushima Graduate School of Medicine, Tokushima, Japan

Correspondence to: Dr M Kunishige, Department of Medicine and Bioregulatory Sciences, University of Tokushima Graduate School of Medicine, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan; kuni@clin.med.tokushima-u.ac.jp

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Acute combined central and peripheral inflammatory demyelination

Generally, inflammatory demyelinating diseases selectively affect either the central or peripheral myelin. Here we report a case of a severe combined central and peripheral demyelination, each of which contributed equally to the clinical syndrome.

Case report

A 32 year old female was admitted to a general district hospital with a 3 day history of aches in the legs, fever (38 °C), urinary retention and leg weakness. Neurological examination revealed a flaccid tetraparesis with abolished abdominal and ankle reflexes, diminished knee reflexes, bilateral extensor plantar responses, and sensory level at T12. The patient was given high dose intravenous prednisone (1 g) for 5 consecutive days. She became bedridden with complete paraplegia of the legs and was referred to our department. Upon admission, in addition to a flaccid tetraparesis (strength 1/5 in the legs and 4/5 to 4 ± 5 in the arms, MRC grade) with abolished abdominal, knee and ankle reflexes, extensor plantar responses, and sensory level at T5, a bilateral gaze evoked nystagmus was detected. Urodynamic examination revealed an atonic bladder. Lumbar puncture revealed a pleocytosis (34/mm³; 84% lymphocytes) and a cerebrospinal fluid (CSF) protein of 132 mg/dl. Neither intrathecal immunoglobulin synthesis nor oligoclonal bands were detected. Complete microbiological and virological investigations on CSF and blood specimens were negative. Further negative findings included serum angiotensin converting enzyme, anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, and

onconeuronal antibodies. Serological testing for anti-ganglioside antibodies (Ganglio-combi test; Bühlmann Laboratories) showed elevated titres for asialo-GM1 (4283 Bühlmann titre units (BTU); normal<1700), GM1 (2855 BTU; normal<1700) and GQ1b (4117 BTU; normal<1700). Magnetic resonance imaging (MRI) of the spinal cord depicted an extensive cervicothoracic myelopathy (fig 1A–D). On MR images of the brain, multiple dot-like cortical and subcortical lesions were delineated, predominantly located in the frontoparietal gray and white matter (fig 1E–G). Electrodiagnostic studies indicated a severe symmetrical demyelinating neuropathy with reduced motor conduction velocities (right peroneal nerve 12.8 m/s, right tibial nerve 16.0 m/s, and right median 44 m/s), prolonged distal latencies (right peroneal nerve 17.1 ms, right tibial nerve 14.5 ms, and right median 5.3 ms), and prolonged or absent F waves, with MUAP displaying temporal dispersion and diminished amplitudes, and with electromyographic signs of acute denervation. The sensory action potentials and conduction velocities were normal.

A whole body computed tomography scan, a salivary gland scintigraphy scan, and a lip biopsy were completely unremarkable. A diagnosis of a combination of acute disseminated encephalomyelopathy (ADEM) and demyelinating polyradiculoneuritis was made. The patient was given 30 g of intravenous immunoglobulin for 5 consecutive days (total 150 g). By day 10 after the start of the immunoglobulin treatment, the patient could stand upright for several seconds with support. As there was no further improvement during the following 2 weeks, the therapy was increased and the patient was treated with a total of six plasma exchanges on alternate days. Five days after the final plasma exchange, the patient could make her first steps with a walker. Six weeks after the final plasma exchange, MRI of the brain and spinal cord showed dramatic regression of the T2 hyperintensities. On follow-up 1 month later, the patient could walk 250 metres with a walker. On examination, no gaze evoked nystagmus was detected. Arm strength was normal. Internal rotation of the hips, hip and knee flexors, and knee extensors were 4/5 on the right and 5/5 on the left; ankle flexors and

extensors and toe dorsiflexors were 4/5 bilaterally. The knee reflexes were sluggish and the ankle reflexes absent. Six months later the patient was able to walk 1000 metres without walking aids. The neurological examination revealed brisk knee and ankle reflexes. The 1 year follow-up showed a patient with normal leg strength and mild ataxia on heel to toe gait. The electrophysiological studies showed improvement of motor conduction velocities (right peroneal nerve 24.1 m/s, right tibial nerve 33.1 m/s, and right median 46.6 m/s) and distal latencies (right peroneal nerve 10.4 ms, right tibial nerve 9.5 ms, and right median 3.4 ms).

Discussion

Our patient presented an acute demyelinating disorder affecting the central and peripheral nervous system simultaneously. After exclusion of other causes, the central nervous system involvement resembled the clinical and radiological characteristics of ADEM with long segmental spinal cord lesion. The peripheral nervous system involvement displayed the clinical, electrodiagnostic, CSF,

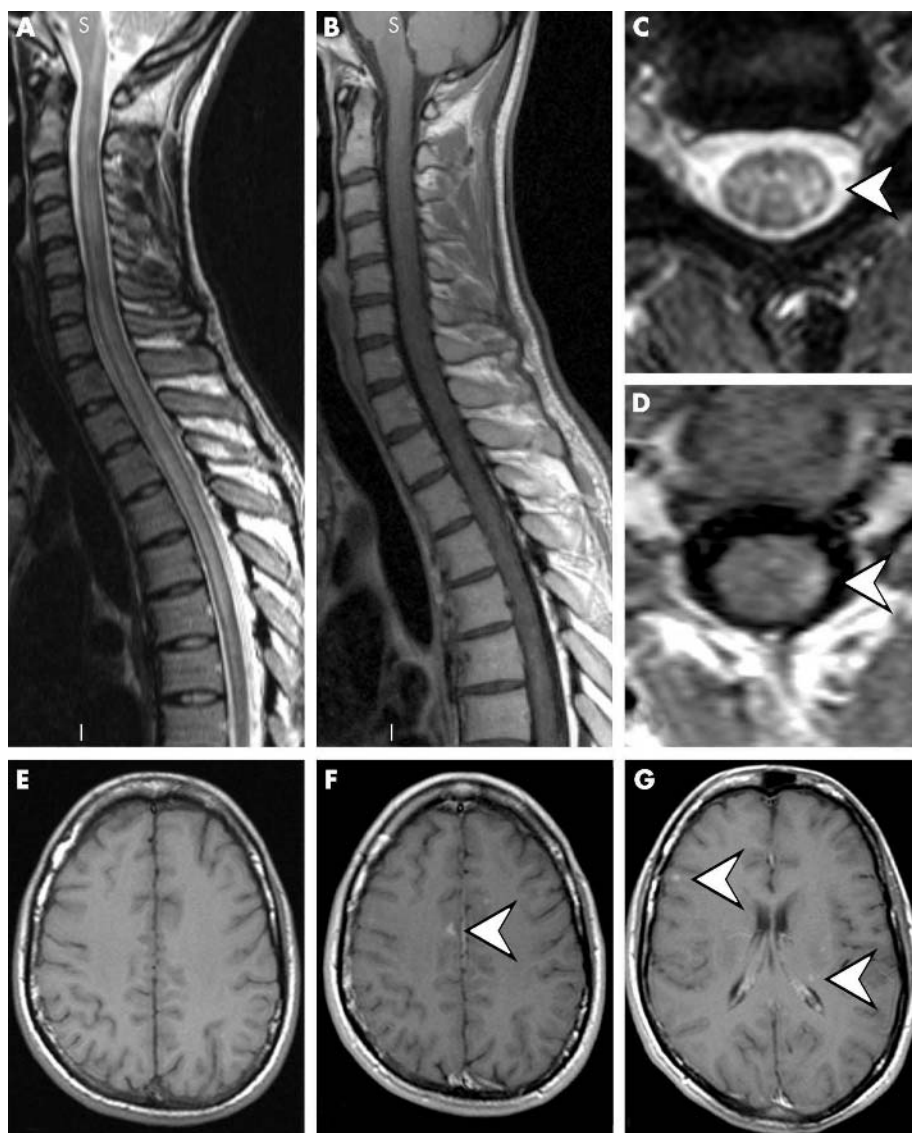


Figure 1 T2 (A, C) and T1 (B, D) weighted, contrast enhanced MR studies of the cervicothoracic spine. Confluent hyperintensities covering all imaged spinal segments are depicted (A), some of which show patchy enhancement (arrows) subsequent to gadolinium administration, predominantly affecting the spinal column dorsolaterally. T1 weighted MR images pre (E) and post (F, G) contrast. Small dot-like cortical and subcortical lesions are seen, showing contrast enhancement (arrows).

and serological features of a demyelinating polyradiculoneuropathy.

Documented overlap of acquired acute central and peripheral system demyelination is very rare. Gamstrop and Blennow used the descriptive diagnosis of encephalomyelodysradiculoneuropathy to designate paediatric cases of Guillain-Barré syndrome with presumed CNS involvement.¹ Again in children, Amit *et al.* coined the entity of acute severe combined demyelination for cases in which central and peripheral nervous system pathology equally contributed to the overall clinical picture.² An acute or subacute combined central and peripheral myelinopathy has been very rarely reported in adults,^{3,4} with no successful treatment regimens being documented.

In our patient, no improvement was seen after high dose intravenous prednisone therapy (5 g), but she dramatically improved on intravenous immunoglobulin and plasma exchange therapy. This finding extends the previous reports of the effectiveness of this therapeutic strategy in the patients with central or peripheral inflammatory demyelination who failed to respond to high dose steroid therapy. Even a delayed treatment (7 weeks after onset of the symptoms) with immunoglobulin induced a significant remission. Further clinical improvement was achieved with subsequent plasma exchange. Our finding supports the concept of immunomodulation using immunoglobulin and plasma exchange in steroid resistant combined central and peripheral inflammatory myelinopathy.

Acute demyelinating diseases are often preceded by an infection or vaccination and considered to be immune mediated. This case of a severe unrestricted demyelinating syndrome encourages the concept that an immunological attack can be directed against central and peripheral myelin in susceptible individuals.

J Katchanov, J D Lünemann, F Masuhr, D Becker, M Ahmadi, J Bösel, R Zschenderlein
Departments of Neurology, University Hospital Charité, Humboldt-University, Schumannstr. 20/21, 10117 Berlin, Germany

S Bamborschke
Department of Neurology, Brandenburg-Klinik, Brandenburgallee 1, 16321 Bernau-Waldsiedlung, Germany

R Klingebiel
Department of Radiology, Neuroradiology Section, University Hospital Charité, Humboldt-University, Schumannstr. 20/21, 10117 Berlin, Germany

Correspondence to: Dr J Katchanov, Klinik fuer Neurologie, Campus Charité Mitte, Schumannstr. 20/21, D-10117 Berlin; juri.katchanov@charite.de

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Miller Fisher syndrome associated with *Pasteurella multocida* infection

Miller Fisher syndrome is characterised by ataxia, areflexia, and ophthalmoplegia and was first described by Charles Miller Fisher in 1956 as an unusual variant of acute idiopathic polyneuritis. There is frequently an antecedent illness¹ and the syndrome is associated with a high titre of anti-GQ1b antibodies in approximately 90% of cases.^{1,2} *Pasteurella multocida* is a Gram negative bacteria, commonly found in the saliva of animals, particularly cats.³

We present the case of a 70 year old lady who developed Miller Fisher syndrome with positive anti-GQ1b antibodies 11 days after *P. multocida* was cultured from a blood sample. Miller Fisher syndrome associated with *P. multocida* infection has not, to our knowledge, been described previously.

Case report

A 70 year old lady presented with a one day history of a painful left hip, fever, sweats, and lethargy following a bite from her pet cat on her left leg on the preceding day. She reported no other recent illnesses. She had had a total left hip replacement four years previously. On examination she was hypotensive and pyrexial with local tenderness of her left hip and decreased range of movement. She had puncture marks on her left shin from the cat bite with surrounding erythema tracking proximally to the groin. Initial blood cultures revealed heavy growth of *P. multocida* sensitive to penicillin. Intravenous benzylpenicillin (1.2 g four times daily) was administered.

The patient's pyrexial illness improved over the next 11 days but then she developed diplopia. The attending orthopaedic surgeon recorded that the cranial nerve examination was normal. By the following day the patient had also become ataxic, and she was referred for a neurological opinion. Examination at this stage revealed marked truncal ataxia and complete internal and external ophthalmoplegia with bilateral ptosis. Limb examination revealed areflexia and ataxia although limb power and sensation were normal. The patient was unable to stand.

A computed tomography brain scan was normal. Magnetic resonance imaging was precluded by claustrophobia. The cerebrospinal fluid was clear, containing 0.5 g/l protein, 3.3 mmol/l glucose, no white cells/mm³, and 255 red cells/mm³. No organisms were seen or cultured. There was no clinical response to pyridostigmine and acetylcholine receptor antibodies were negative. A sample of blood taken seven days after the onset of neurological symptoms was positive for anti-GQ1b antibodies at a titre of 1:1600 using enzyme-linked immunosorbent assay (ELISA). The testing laboratory considered a titre above 1:100 to be positive for anti-GQ1b antibodies. Other antiganglioside antibodies and follow up anti-GQ1b antibodies were not tested.

A diagnosis of Miller Fisher syndrome was made and intravenous immunoglobulin

(0.4 g/kg daily for five days) was administered with gradual improvement in symptoms and signs over the next six weeks leading to the patient's discharge. At follow up five months later she had fully recovered.

Discussion

This patient developed the typical neurological symptoms of Miller Fisher syndrome with positive anti-GQ1b antibodies 11 days after *P. multocida* was cultured from a blood sample. To our knowledge this is the first reported case of any form of Guillain-Barré syndrome associated with *P. multocida* infection.

P. multocida is a small Gram negative coccobacillus⁴ and is an important animal and human opportunistic pathogen. In humans it can cause soft tissue, respiratory, urinary tract, and meningeal infections. The mechanisms by which *P. multocida* might cause Miller Fisher syndrome (we are assuming causation and accept we have only demonstrated temporal association) are unknown but molecular mimicry is a possibility. There is considerable evidence supporting the theory of molecular mimicry between lipopolysaccharide (LPS) from *Campylobacter jejuni* and the GQ1b ganglioside.⁵ As *P. multocida* is Gram negative, its capsule similarly has LPS. However, we were unable to find any research specifically suggesting a similarity between the *P. multocida* LPS and the GQ1b ganglioside. *P. multocida* has previously been reported in association with acute disseminated encephalomyelitis⁴ but not, to our knowledge, with any other diseases with a presumed autoimmune basis.

Although an antecedent illness has frequently been noted before the onset of Miller Fisher syndrome the causative agents are not as well described as in Guillain-Barré syndrome.⁵ While *C. jejuni* has been implicated in the pathogenesis of Miller Fisher syndrome following enteritis, a recent study¹ of 50 patients with the syndrome found that 76% had respiratory symptoms in the month preceding onset of the syndrome compared with only 4% with gastrointestinal symptoms. *Haemophilus influenzae*, *Staphylococcus aureus*, *Mycoplasma pneumoniae*, *Coxiella burnetii*, cytomegalovirus, Epstein-Barr virus, varicella zoster, and mumps virus have also been reported as antecedent agents in Miller Fisher syndrome. However, a statistical correlation with Miller Fisher syndrome has only been shown for *M. pneumoniae*⁵—serological evidence of recent infection was found in 7% of Miller Fisher patients compared with 2% of patients with Guillain-Barré syndrome.

From the above discussion it is clear that the antecedent illness in Miller Fisher syndrome commonly takes the form of a respiratory infection of unknown aetiology. *P. multocida* can cause respiratory infection. It is often difficult to isolate this organism from sputum samples³ and it has been reported as causing indolent and asymptomatic pulmonary infection,³ including asymptomatic lung abscess. For these reasons *P. multocida* infection is possibly underdiagnosed. Therefore, while we believe this is the first reported case of an association between Miller Fisher syndrome and *P. multocida* we believe it highly unlikely to be unique.

L P Bennetto

Institute of Clinical Neurosciences, University of Bristol, Glial Cell Research Laboratory, Frenchay Hospital, Bristol, UK

P Lyons

Department of Neurology, Royal United Hospital, Bath, UK

Correspondence to: L P Bennetto; luke.bennetto@bris.ac.uk

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Coagulopathy and NICE recommendations for patients with mild head injury

Management of patients with mild head injury (MHI) is open to debate.¹ In the last few years, there has been a trend towards earlier diagnosis, implying an extensive use of computed tomography (CT), rather than admission and observation. The National Institute for Clinical Excellence (NICE) has recently proposed new evidence based recommendations on all steps of the management of patients with MHI.² In the diagnostic algorithm, coagulopathy (history of bleeding, clotting disorder, or current treatment with warfarin) is not considered a predictor variable necessitating early CT in subjects without loss of consciousness (LOC) or amnesia since injury. This statement conflicts with previous guidelines, where history of coagulopathy, independently of symptoms, indicated CT.³

Since 1999, all cases with MHI attending the Emergency Department of our district hospital have been treated and registered in a comprehensive database according to predefined procedures.³ Our criteria for CT and/or hospital admission are wider than the NICE criteria; in particular, there is routine detailing of NICE variables, but in addition, all subjects with coagulopathy have an early CT, independently of symptoms and signs after injury. This provides the opportunity to determine the risk related to coagulopathy and the accuracy of the NICE recommendations.

We analysed the data of 7955 consecutive patients within 24 hours from trauma, who had been triaged for an acute MHI. MHI was defined as an injury of the head, other than any superficial injury to the face, Glasgow Coma Score (GCS) definitely 14 or 15, in subjects aged ≥10 years. We excluded 1258 more patients because of unclear history of the trauma as primary event, major trauma with unstable vital signs, GCS <14, penetrating injuries, pregnancy, or voluntary discharge. All patients re-attending for complaints after discharge (282 cases) underwent a CT scan and in this study were considered only once. All patients received

written recommendations at discharge for home observation and complaints that would require referral back to hospital for further evaluation. Observers were instructed to check for symptoms and signs, and for any change in patients' clinical status for 7 days.

According to NICE, CT scan is recommended in the presence of: (a) GCS <13 at any point and/or equal to 13 or 14 at 2 hours after injury, (b) any sign of basal skull fracture, (c) any focal neurological deficit, (d) post-traumatic seizure, (e) vomiting (>one episode), and (f) amnesia of events before impact >30 minutes, (g) risk factors (coagulopathy, age ≥65 years, dangerous mechanism of injury), provided that patients have experienced some LOC or amnesia since injury. In our protocol,⁴ CT is mandatory for subjects with risk factors, in particular amnesia and/or LOC (but excluding old age), independently of signs and symptoms.

Following our protocol, 4081 out of 4547 (89.8%) eligible patients had an early CT scan. In 3580 early CT was also indicated according to the NICE protocol; in 501, CT scans were performed in subjects outside the NICE protocol. These patients had CT because of coagulopathy (warfarin therapy) in 66 cases (13.2%), diffuse headache in 178 cases (35.5%), previous neurosurgical intervention in 26 cases (5.2%), history of seizures in 22 cases (4.4%), dangerous mechanism of injury in 172 cases (34.3%), and recent alcohol and/or drug misuse in 58 cases (11.6%).

Clinically important intracranial lesions were demonstrated in 477/3580 (13.3%) patients of the NICE group. Neurosurgical intervention was required within 7 days in 97 patients (2.7%) for haematoma evacuation or for elevation of depressed skull fracture. At follow up (6 months), 36 patients (0.1%) had an unfavourable outcome (death, persisting vegetative state, or severe disability by the Glasgow Outcome Scale), rated by an expert physician on the basis of a structured telephone call.

In the 501 NICE negative cases, 40 patients (8.0%) had an intracranial haemorrhagic lesion: intracerebral haematoma (20 cases); intracerebral haematoma plus subarachnoid haemorrhage (2); intracerebral haematoma plus subdural haematoma (3); subarachnoid haemorrhage (2); subarachnoid haemorrhage plus subdural haematoma (1), subdural

haematoma (11); and epidural haematoma (1). This prevalence is lower compared with NICE positive cases (Fisher's exact test, p = 0.0006), but nevertheless NICE recommendations would not have led to early detection of these 40 lesions, for which neurosurgical intervention was required in five (12.5%): intracerebral haematoma evacuation (1 case), subdural haematoma (3), subarachnoid haemorrhage plus subdural haematoma (1). At follow up, only one patient died after 9 days for causes related to intracerebral haematoma, the remaining having a favourable outcome. In these 40 NICE negative cases with haemorrhagic lesions, coagulopathy was the main factor leading to CT scan in 16 cases (40%), and was associated with a fivefold increase in the risk of intracranial lesions (table 1). With logistic analysis, coagulopathy was the only predictor variable associated with CT lesions in asymptomatic patients not fulfilling NICE criteria for early CT. Six patients, re-evaluated for complaints after a median (interquartile range) time of 144 hours (66 to 168), had an intracranial lesion detected by a second CT; four belonged to the NICE positive group, two were in the NICE negative. None had coagulopathy.

The post hoc analysis of our prospective database demonstrates that NICE recommendations for CT scanning identify the majority of patients with intracranial lesions in subjects attending the ED for MHI. However, the exclusion of coagulopathy as a factor always indicating CT impairs the diagnostic accuracy of NICE guidance. Routine use of CT scanning is not cost effective; more than 90% of CT scanning are negative in subjects with MHI, and at least 98% are negative for epidural haematoma, the event requiring immediate intervention. A more liberal policy for CT use, making CT mandatory in patients with coagulopathy, independently of head trauma severity, would indicate only 66 additional CT in our total cohort of 3581 (less than 2.0%), with a 1:4 probability of identifying an intracranial lesion.

The indications for CT use in MHI are subject to a continuous debate.³ Our data strongly suggest that the restrictive use of CT proposed by NICE in the presence of risk

Table 1 Characteristics of the 501 patients, submitted to early CT scan according to protocol, and not considered by NICE recommendations

	CT negative (n = 461)	CT positive (n = 40)	Odds ratio (95% CI)	P value*
Median (IQR) age, years	53 (29 to 77)	68 (46 to 78)	-	0.054
Median (IQR) INR†	2.3 (2.0 to 2.8)	2.2 (2.2 to 2.6)	-	0.464
Cause of injury				
Fall	204 (44.3%)	19 (47.5%)	1.14 (0.59 to 2.18)	0.741
Crash	179 (38.8%)	15 (37.5%)	0.94 (0.48 to 1.84)	1.000
Assault	15 (3.3%)	2 (5.0%)	1.56 (0.34 to 7.10)	0.637
Occupational	32 (6.9%)	2 (5.0%)	0.71 (0.16 to 3.06)	1.000
Risk factors				
Coagulopathy	50 (10.8%)	16 (40.0%)	5.48 (2.73 to 11.00)	<0.001
Dangerous mechanism	156 (33.8%)	16 (40.0%)	1.30 (0.67 to 2.53)	0.488
Age ≥65 years	191 (41.4%)	22 (55.0%)	1.73 (0.90 to 3.31)	0.133
History of epilepsy	20 (4.3%)	2 (5.0%)	1.16 (0.26 to 5.15)	0.692
Previous neurosurgery	26 (5.6%)	1 (2.5%)	0.43 (0.06 to 3.25)	0.713
Alcohol and/or drugs	51 (11.1%)	7 (17.5%)	1.71 (0.72 to 4.05)	0.205

CI, confidence interval; *Mann-Whitney U test or Fisher's exact test: p<0.05; †international normalised ratio in patients with coagulopathy.

factors may be generally accepted. However, in the light of our data we suggest that CT should also be considered for all subjects with coagulopathy.

A Fabbri, A Vandelli

Dipartimento Emergenza-Urgenza Accettazione,
Ospedale Morgagni-Pierantoni, Azienda Unità
Sanitaria Locale di Forlì, Italy

F Servadei

Unità Operativa di Neurochirurgia per la
Traumatologia, Ospedale M Bufalini, Azienda Unità
Sanitaria Locale di Cesena, Italy

G Marchesini

Alma Mater Studiorum, Università di Bologna, Italy

Correspondence to: Dr A Fabbri, Dipartimento
Emergenza-Urgenza Accettazione, Ospedale
Morgagni-Pierantoni, Azienda Unità Sanitaria Locale
di Forlì, via Forlanini 34 - I - 47100 Forlì, Italy;
andfabbri@libero.it

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Neurogenic T wave inversion in pure left insular stroke associated with hyperhomocysteinaemia

Alterations in cardiac depolarisation and repolarisation are reported in 74% of patients with cerebrovascular events.¹ They are more frequent after subarachnoid and intracerebral haemorrhage, but may also occur in acute ischaemic stroke (15–30%) and are related to an increased incidence of malignant arrhythmia and sudden death (6%).²

The most common ECG alterations are QT prolongation, ST segment alterations, T wave flattening or inversion, and abnormal U waves.¹ ECG changes may be similar to those commonly observed in patients with coronary artery disease,² but they have also been demonstrated in the absence of autopsy proven heart disease.¹ This suggests a neurogenic rather than a primary cardiac cause, mediated by unbalanced autonomic control.

Experimental evidence implicates the insular cortex in cardiovascular control and heart chronotropic organisation,² and suggests its involvement in the genesis of adverse neurogenic ECG alterations.

Case report

A 68 year old right handed female was admitted after the acute onset of mild right ataxic hemiparesis, right facial and hypoglossal nerve palsy, and dysarthria. The patient was vegetarian, had no history of diabetes or cardiac disease, and was a non-smoker without relevant family history. Blood pressure was 150/100 mm Hg and heart rate (HR) was 94 beats per minute (bpm). The admission brain CT and Doppler ultrasounds were normal. A left anterior hemiblock was detected at ECG (fig 1C).

Standard blood chemistry showed macrocytic anaemia, with other parameters within normal range, including serum lipids (lipoprotein a, total, HDL, and LDL cholesterol, and triglycerides). Antithrombin III, PT, PTT, fibrinogen, protein C and S activity, and activated protein C resistance were normal. Searches for lupus anticoagulant, antinuclear antibodies, antibodies to extractable nuclear antigens, anti-neutrophil cytoplasm auto-antibodies, anticardiolipin antibodies, and cryoglobulins were negative.

A homocysteine serum level of 35.7 $\mu\text{mol/l}$ (normal values: <20 $\mu\text{mol/l}$), vitamin B12 deficiency (90 pg/ml; normal values: 200–1000 pg/ml), and normal folic acid were detected. Vitamin B12 and antiplatelet therapy were started. The patient's clinical condition improved and 5 days later she was discharged.

The day after discharge she was readmitted because of the recurrence of moderate right ataxic hemiparesis, dysarthria, and non-fluent aphasia with phonemic paraphasia, anomia, and with essentially preserved comprehension and repetition. Blood pressure was 130/90 mm Hg and HR was 92 bpm. Blood examination showed the previously detected macrocytic anaemia, and a C reactive protein (CRP) value of 2.14 mg/dl (normal value: <0.8 mg/dl). Brain CT and MRI (fig 1A and B) showed an infarct limited to

the left insular cortex with no other lesions on the diffusion weighted images.

The admission ECG showed a global T wave inversion (fig 1D), which persisted on subsequent monitoring, and disappeared only after 2 months. No other ECG alterations were detected, including QT prolongation (QT = 0.34; QTc = 0.42 s). The patient had no cardiac symptoms and transthoracic echocardiography was normal as was serum potassium, calcium, and cardiac enzyme (creatine kinase-MB, troponine I, and myoglobin) investigation repeated over 5 days.

Following 3 weeks of therapy, vitamin B12 and homocysteine levels were normal, CRP value was 1.87 mg/dl, and the macrocytic anaemia had improved.

By 2 months after the cerebrovascular events, macrocytic anaemia was absent, homocysteine, vitamin B12, and CRP were normal, and the ECG had nearly normalised. An adenosine-thallium scan performed 6 months after stroke onset showed no evidence of coronary artery disease. To date there have been no cardiac events.

Comment

Acute insular stroke may present with various clinical presentations, due to the anatomic and functional complexity of the insular lobe and its wide connections with the frontal, temporal, parietal, and olfactory cortex, and with the basal ganglia, thalamus, and limbic structures.^{3,4} It is an important gustatory, somatosensory, and visceral motor sensory processing area, a component of the vestibular and limbic cortex, and is implicated in pain processing, volitional swallowing, cardiovascular control, and cerebrogenic sudden death.^{2–4}

Pure insular strokes, rare entities in clinical practice, are defined as infarcts restricted to the insula in which coexisting brain lesions are exclusion criteria, with the exception of some involvement of the claustrum and capsula externa.⁴ This definition is justified by the complex insular arterial supply which principally supplies the insular cortex, the capsula externa, and the claustrum, and, sporadically, the capsula externa.⁴

The prominent clinical features of our case were neuropsychological disorders (expressive aphasia, dysarthria, verbal memory impairment), and electrocardiographic alterations, represented by persistent T wave inversion.

Neurogenic ECG alterations are often transient, but cause diagnostic problems, mimicking acute myocardial infarction. Some features of T waves may be suggestive of heart pathology, but they are non-specific, making it important to consider a neurogenic genesis to avoid unsuitable therapies.

The neurogenic nature of T wave inversion in our case was demonstrated by the lack of evidence of coronary artery disease or cardiac pathology, both of which were ruled out by echocardiography and adenosine-thallium scan. Myocardial enzymes, which have also been reported to be elevated mainly in large size stroke, were normal probably because of the limited extent of cerebral infarction.

In insular stroke the pathophysiology of abnormalities of rate, rhythm, and conduction is related to an imbalance of autonomic cardiovascular control and to increased circulating and local myocardial tissue catecholamines, suggesting an underlying sympathetically mediated mechanism. The insular cortex has been shown experimentally

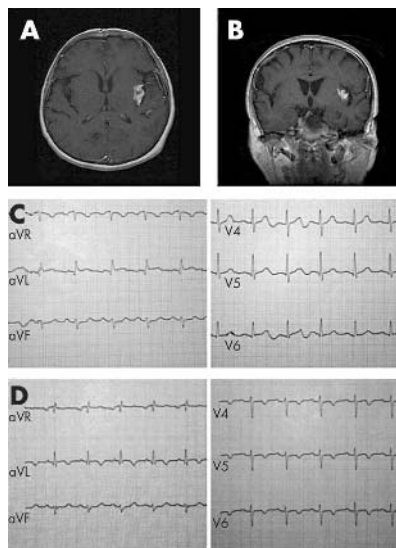


Figure 1 (A, B) T1 weighted spin echo axial and coronal scan (repetition time, TR = 500 ms; echo time, TE = 10 ms), showing the pure left insular stroke; (C) admission ECG showing only a left anterior hemiblock; (D) ECG performed 7 days after the second stroke showing the presence of neurogenic T wave inversion.

to contain an arrhythmogenic centre implicated in neurogenic electrocardiographic changes.²

There is evidence of cortical asymmetry in the regulation of cardiovascular functions: the left insula is concerned mainly with control of parasympathetic cardiac drive, and the right with control of cardiovascular sympathetic tone.^{1,2} Damage to the left insular cortex by stroke may shift sympathovagal balance towards increased basal sympathetic tone (a pro-arrhythmic condition), with a decrease in the randomness of HR variability, and may contribute to the excess cardiac mortality following stroke.^{1,2}

Insular infarcts so far reported are caused by artery to artery or cardiac embolisms.⁴ To our knowledge this is the first reported case of insular stroke associated with hyperhomocysteinaemia, which is an emerging independent risk factor for stroke and for vascular recurrence after ischaemic stroke.⁵

In conclusion, persistent neurogenic T wave alteration due to a left insular infarct associated with hyperhomocysteinaemia is reported in this paper. The case underlines the functional complexity of the insular cortex, its role in the generation of cardiovascular changes, and the importance of cardiac monitoring in stroke patients.

J Mandrioli, A Zini, M Cavazzuti, P Panzetti

Department of Neuroscience, University of Modena and Reggio Emilia, Modena, Italy

Correspondence to: Dr Jessica Mandrioli, Neurological Clinic, Department of Neuroscience, University of Modena and Reggio Emilia, Policlinico di Modena, Via del Pozzo n. 71, 41100 Modena, Italy; jessicamandrioli@hotmail.com

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Prion disease at a regional neuroscience centre: retrospective audit

Timely diagnosis of prion disease is vital if appropriate information and psychosocial support is to be made available to patients and families and appropriate arrangements made for symptomatic treatment and provision of palliative care. For many of these issues optimal management remains uncertain. Guidelines have been published by the Creutzfeldt–Jakob disease (CJD) Support Network¹ suggesting that a “carefully coordinated multidisciplinary team” is required to provide a “flexible, family-centred approach, with specialist CJD and palliative care services”, with appointment of a keyworker “as soon as possible” to tailor appropriate response. The optimal location of the

palliative care is acknowledged to depend on individual circumstances, but it is recognised that “acute neurology or psychiatric units cannot provide the appropriate environment for longer term care”. The guidelines explicitly do not address general palliative nursing care issues.

Most reports on cohorts of patients with prion disease have emanated from national referral centres. However, it is widely accepted that delivery of patient care close to or at home is the ideal. In many cases, this means regional neurological facilities. We undertook an audit of all pathologically confirmed prion disease cases seen in the catchment area of the Walton Centre for Neurology and Neurosurgery (WCNN), a regional neuroscience centre in Liverpool, UK, serving a population of around 3 million people and 14 district general hospitals (DGHs) in northwest England and north Wales, over a 12 year period (1990–2001) prior to publication of the CJD Support Network guidelines, to ascertain what management plans had been formulated or implemented for patients with prion disease.

Cases were identified through individual consultant neurologists and from the National Creutzfeldt–Jakob Disease Surveillance Unit (NCJDSU) in Edinburgh (Professor R G Will, personal communication). Symptomatic interventions and management of the terminal phase of the illness were ascertained by case note review, in particular, decisions about patient hydration and “do not resuscitate” (DNR) orders.

From 1990 through 2001, 82 patients with suspected CJD were referred from the Mersey Region to the NCJDSU (41 males, 41 females; average age 60.1 (SEM 19.7) years, range 14–90; eight patients ≤ 30 years). Of these, 65 referrals were made after 1995 when the epidemic of variant CJD (vCJD) in the UK began. A total of 66 patients (80%) presented initially to non-neurologists and 44 referrals were of inpatients at WCNN, usually transferred from DGHs by visiting neurologists. A total of 38 cases were referred to NCJDSU directly from DGHs or from Alder Hey Children’s Hospital, Liverpool.

Prion disease was confirmed pathologically in 43/82 referrals, giving an overall diagnostic accuracy of 52%. Of the cases with confirmed prion disease, 33 had sporadic CJD, 8 had vCJD (some already reported^{2,3}), and 2 had iatrogenic disease. There were no familial cases. Three patients never saw a neurologist. Of the 39 non-prion cases, eight were found to have alternative diagnoses only at post mortem, principally Alzheimer’s disease and dementia with Lewy bodies.

In none of the 43 cases with pathologically confirmed prion disease could a keyworker coordinating care be identified from case note review. Various symptomatic treatments for myoclonus, the commonest movement disorder, were tried, namely sodium valproate, clonazepam, baclofen, diazepam, and phenytoin. An empirical course of steroids to treat an undiagnosed vasculitis or autoimmune disease was given in a few cases, without benefit.

It was recorded in the notes of 32 patients (75%) that when oral fluid intake proved insufficient, fluids were given by the subcutaneous, nasogastric, or intravenous route to maintain adequate hydration. The families of only two patients opted to have a percutaneous endoscopic gastrostomy (PEG) tube placed: in one patient this continued to be in use for nearly three years, in the other, only for a period of weeks before death.

Various symptomatic treatments were used to relieve distress in the terminal phase of disease, namely diamorphine, midazolam, and cyclomorphine. In only nine cases (21%) was there any comment about cardio-respiratory resuscitation policy. In seven cases it was explicitly stated that the patient was not for resuscitation; in one case the family did not agree to a DNR policy, and in one case it was not clear what policy, if any, was agreed. All the patients died in hospital; none went to a hospice. One patient with sporadic CJD temporarily went to a nursing home, before returning to hospital to die. Nursing home placement was considered for one other patient, but the family preferred the patient to stay in hospital.

Although there are hopes for the efficacy of agents such as mepacrine and PPS, disease modifying treatment for prion disease does not currently exist. Hence, once the diagnosis is made, management is symptomatic (for example, for movement disorders, especially myoclonus, seizures, autonomic and sleep disorders, swallowing problems, and pain) and care is palliative. This being the case, provision of information and psychosocial support is of paramount importance. In the UK, patients and carers may contact various resources, such as the NCJDSU and the National Care Co-ordinator,⁴ the National Prion Clinic, the CJD Support Network, the Human BSE Foundation, and the CJD Advice Network (Department of Health). However, these agencies may not be able to provide local solutions to the care needs of patients and families affected with prion disease. Difficulties in finding appropriate locations for palliative care of patients with vCJD have been documented,⁵ leading the Department of Health to create a National Care Package.⁴

The heterogeneity of management revealed by our audit most likely reflects uncertainty about the optimal management of prion disease, and the absence of specific guidelines during the time covered by the audit. The development of guidelines and integrated care pathways which can address the specific issues facing patients with prion disease and their relatives in a comprehensive yet flexible manner may be helpful, although again disease rarity suggests that completing the audit cycle may be a long process. Coordination and support from at least one dedicated health professional in each regional neuroscience centre, to ensure implementation of guidelines¹ and to work with local agencies such as palliative care teams, currently seems an appropriate response.

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A J Larner, M Doran

Cognitive Function Clinic, Walton Centre for Neurology and Neurosurgery, Liverpool, UK

Correspondence to: Dr Larner, Cognitive Function Clinic, Walton Centre for Neurology and Neurosurgery, Lower Lane, Fazakerley, Liverpool, L9 7LJ, UK; a.larner@thewaltoncentre.nhs.uk

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BOOK REVIEWS

Myopathies in clinical practice

Edited by Phillip R J Barnes and David Hilton-Jones. Published by Martin Dunitz, London, 2003, £49.95 (hardcover), pp 161. ISBN 1-899066-71-3

Text books come in two forms; some attempt to tell you all there is to know while others try and tell you what you need to know. The editors' introduction to this book suggests that it falls into the latter category but in fact it "punches above its weight" with regard to the depth of coverage in a number of the chapters and includes observations, reminders, and pointers that all myologists, let alone general neurologists, will find extremely valuable.

Beyond the superficial level, neuromuscular disorders are complicated mainly because we now know so much about their underlying molecular biology. This book goes as far as reasonably possible in making these complexities understandable. It is divided into two sections. The first deals with basic principles, including clinical assessment and the investigation of muscle disease. The writing style is direct and almost conversational—in the style of a tutorial, which many

will find attractive. The section on investigation of muscle disease is particularly clear and comprehensive with a helpful exposition on the basics of electromyography in muscle disease and neuromuscular transmission disorders. This section concludes with a chapter on the principals of therapy of neuromuscular disease—a topic which is usually tucked away in the back of a more typical text book—perhaps reflecting the Editors very positive attitude to this aspect of this speciality. To quote them, to say that there is "nothing that I can do for you" is indeed a sad reflection on the lack of a holistic or rehabilitative approach from the clinicians involved.

The second section deals in turn with the muscular dystrophies, inflammatory myopathies, muscle channelopathies, metabolic myopathies, and the toxic and endocrine myopathies, and concludes with chapters on congenital myopathies and miscellaneous muscle disorders. The final chapter on neuromuscular junction disorders is included for the sake of completeness. Each of these chapters is to a similar high standard, although I would comment that there is no obvious logic in the way that these are ordered in the book. There is also a comprehensive index that proves efficient on several occasions.

This volume is commendably short and the text is arranged in a double column format. The production is lavish, profusely illustrated in colour with many diagrams and text boxes, which are beautifully clear. For general neurologists, I think this book will have few serious rivals as a convenient, modern, and comprehensive source of information on the most important aspects of muscle disease, and I can recommend it most highly.

R J M Lane

The central nervous system structure and function—third edition

Edited by Per Brodal. Published by Oxford University Press, Oxford, 2003, £49.50 (hardback), pp 495. ISBN 0-19-516560-8

This third edition of Per Brodal's book "*The central nervous system: structure and function*",

last edited in 1998, attests to the efforts of the author to keep up with the rapid pace of development in the field of neurosciences. Many of us probably remember the repulsive effect of overwhelming details in some textbooks of neuroanatomy or neurophysiology, that fail to be relevant in clinical practice. Here, the dynamic and concise presentation of both the structure and the function of the central nervous system at different levels (molecular, cellular, and systems), with special emphasis on how the different components are connected and interact, manages to captivate the reader. Beside key information on the fundamental background, there are numerous clinical examples that will help the medical student to bridge the gap between basic and clinical neuroscience. The book also offers several didactic drawings and figures, and, for the reader interested in a particular topic, more detailed sections are placed in highlighted boxes. In addition, a rich selection of references recommended by the author on each topic are listed at the end of the book. The third edition includes two new sections on the vestibular system and the control of eye movements.

The principal aim of the author, who perpetuates a familial tradition (the first Norwegian edition of the book was run by Per Brodal's father in 1949), is "to stimulate understanding rather than memorization of isolated facts" and "[to foster] a realistic attitude toward our still limited ability to explain the marvels of the human brain."

I recommend this book to all medical students, and also to more advanced clinicians who wish to refresh their knowledge in basic neurosciences or as a useful tool for teaching their younger colleagues.

S Debette

CORRECTION

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In the Letter by Jardine et al (*J Neurol Neurosurg Psychiatry* 2004;**75**:1651) the initials of Krediet were published incorrectly. The correct initials are C T P.