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. Peripheral neuropathy occurs in up to 20% of these patients and is usually asymptomatic. Neurophysiological findings are consistent with primary axonal polyneuropathy. 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 right foot. 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 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 right foot. 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.

Laboratory investigations included a polyclonal increase in IgM component, with a low concentration band in the slow γ region. Serum immunofixation confirmed the presence of IgG. 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, antineuclear 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 (10 cells/μl), Gram stain, Lyme antibody titre, and Lyme 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 centrifugal nodules, with thickening of the interlobular septa, and no hilar lymphadenopathy, which was consistent with sarcoidosis. Pulmonary function tests were normal. Abdominal fat pad aspiration biopsy was negative for amyloid. A right sural nerve biopsy revealed non-casing 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.

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-casing granulomas in the epineurium of the right sural nerve. Although previous cases of pure sensory polyneuropathy have been reported, they were distinct from our case in that the patients were already diagnosed with systemic sarcoidosis,1, 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, 3 The relative frequency of different subtypes of sarcoid neuropathies is uncertain. In a detailed clinical description of 10 cases of chronic sensory polyneuropathy, peripheral neuropathy was the most common form of non-cranial neuropathy.1 Other patterns included small fibre neuropathy, acute ascending paralysis similar to Guillain–Barré syndrome, polyradiculopathy, and lumbo-sacralplexopathy.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.1 Alternatively, ischaemia induced by necrotising vasculitis1 and direct mechanical compression of nerve fibres may lead to primary axonal degeneration,1 as supported by pathological findings of non-casing granulomas in the epineurium and perineurium with periangiitis, panangiitis, perineuritis, and axonal loss.3 Furthermore, most neurophysiological findings were consistent with an axonal form of nerve injury.1, 4, 5 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.

Acknowledgements

The authors acknowledge Dr T Hillel-Wrayte for assistance with the figure.

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, 53 Fruit St, Boston, 02114, MA, USA; PSAIO@PARTNERS.ORG

doi: 10.1136/jnnp.2003.028134

References


www.jnnp.com
Non-herpetic limbic encephalitis associated with relapsing polychondritis

Relapsing polychondritis 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 polychondritis 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 inappropriate affectual focus, disintegrated 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 with vague margins in the medial temporal lobe, hippocampus, and insular cortex (fig 1A).

Laboratory studies showed white blood cell count 14.8 x 10⁹/L (normal 3.9–9.3 x 10⁹/L), platelet count 363 x 10⁹/L, β-thromboglobulin (β-TG) 94 µg/L (normal <50 µg/L), platelet factor 4 (PF-4) 30 ng/mL (normal <20 ng/mL), erythrocyte sedimentation rate (ESR) 42 mm/h, C reactive protein (CRP) 29 mg/L, ferritin 668 µg/L (normal <465 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. Serum creatinine and vitamin 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. Cerebrospinal fluid (CSF) was sterile, with a protein concentration of 86 mg/dL; glucose, 3.0 mmol/L (serum glucose, 5.5 mmol/L); white cells, 8 x 10⁹/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 methylprednisolone, 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, IgG 1570 IU/L, fibrinogen 5.51 g/L, and ferritin 448 µg/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 x 10⁹/L (83% lymphocytes), protein 46 g/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 methylprednisolone 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. MRI showed no evidence of a neoplasm or a known autoimmune disease was found.

Several previous case reports of relapsing polychondritis include confusion, disorientation, and psychiatric symptoms with or without neurological abnormalities, 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, an inflammatory cell component has been demonstrated.

In our patients, simultaneous brain and auricular biopsies showed active inflammation with chondritis and meningoencephalitis. The inflammatory cell components were consistent with meningoencephalitis and 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 confusion 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, a partially 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, 7-43-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan; tyamada@fukuoka-u.ac.jp
doi: 10.1136/jnnp.2003.035170
Competing interests: none declared

References

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 oriented 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

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 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 on brain MRI and cerebrospinal fluid findings. Although he now requires bilateral assistance 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) sequence1 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.,4 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 Olgettra, 60, 20132 Milan, Italy; m.filippi@srsr.it
doi: 10.1136/jnnp.2004.042069
Competing interests: none declared

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.
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 Homer’s syndrome. Elevation of the right upper eyelid was slow but intact. 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 was 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. The 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 Homer’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 Frenzel’s glasses. He noted 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 the cerebellum and tonsil6 and with a demyelinating lesion of the superior and inferior cerebellar peduncles.4 Lee et al reported a patient with lateral medullary infarction who showed a gaze evoked horizontal nystagmus as well as axial lateropulsion.1 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 spinothalamocortic sensory deficit, which in some cases appears a few days after the onset of other symptoms.3 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 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 vestibulo spinal 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., 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 the loss of function 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-mh@seirei.or.jp
doi: 10.1136/jnnp.2003.035246

References

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, carried 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 in determining epilepsy. 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, 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 cesarean section after an uneventful pregnancy. During follow up, physical and neurologic examinations revealed normal neurological development and physical growth. Neuropsychology was highly suggestive of an occipital origin; seizures were characterized by visual phenomena (blackouts), 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, Kyte et al 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 intraindividual 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 Mxs2 mutant mice with seizures accompanied by abnormal development of the cerebral cortex, 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, 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.

Acknowledgements
The authors thank Dr S Blaser for reviewing the manuscript and her important contribution to the neuroimaging analysis.

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; kelvale@msn.com; kdvalente@usp.br

doi: 10.1136/jnnp.2004.035733

Competing interests: none declared

References
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 myotic (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 mollity 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. After 2 min of 60° head up tilt, mean BP was 46 mm Hg (111 (4) mm Hg), HR 110 bpm (75 (4) bpm), and MSNA 84 bursts/min (31 (4) bursts/min). After 2 min of 60° head up tilt, mean BP was 46 mm Hg (111 (5) mm Hg), HR 123 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 demonstrated complete remission. Her gastrointestinal symptoms improved, and the 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, and (c) autonomic dysfunction including Holmes-Adie pupils and impaired baroreflex modulation of heart rate and vasoconstriction, and (d) enteric neuropathy causing gastrointestinal dysmotility. 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. 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 polynuropathy 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 neurons and certain tumours including small cell lung carcinoma and neuroblastoma which share a common ectodermal origin. 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. 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 autoimmune recognised so far is directed at postsynaptic acetylcholine receptors in autonomic ganglia, and was not detected in our patient.

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. Baroreflexes 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. We hypothesise that baroreflex failure caused severe postural hypotension by two mechanisms: firstly, the immediate vasconstrictor and AVP responses to changes in central blood volume were decreased; and secondly, increased sympathetic activity at rest mediated chronic splanchic 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.

Acknowledgements

We are grateful for the assistance of Professor Vanda A Lennon, Mayo Clinic, Rochester, MN who undertook paraneoplastic autoimmune screening and identified the ANNA-1 antibody. Dr Carina Miles reported the tumour biopsy. The figure was prepared by The Department of Medical Illustration, Christchurch Hospital, New Zealand.

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
doi: 10.1136/jnnp.2003.034827

References


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.

Case report

Our patient was a 52 year old left handed 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 epigastrum was painful on palpation. He was stuporous, 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 oculocoephalic 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 dossier had been lost but the hypotonia 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 stuporous, 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. Voevoal 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 weeks 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.

Discussion

Although new anti-NMDA receptor antibodies have been described (and in the following few days, our patient was found to have such antibodies), our patient is unique in that he presented with ocular motor apraxia. This presents a challenge in the differential diagnosis, as ocular motor apraxia is usually caused 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 is 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.

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. Acquired ocular motor apraxia is usually caused by...
bihemispheric infarcts. 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. Bilateral damage to the PEFs may result in severe impairment of pursuit movements. The posterior cingulate cortex (PCC)—which is known to show neuronal activity during pursuit movements—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.

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.

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.

References