LETTERS TO THE EDITOR

A case of pandysautonomia with associated sensory ganglionopathy

Since Young *et al*[1] described a patient with acute loss of sympathetic and parasympathetic functions in 1969, many similar cases have been reported as being acute idiopathic autonomic neuropathy.[2] Apart from acute cholinergic neuropathy, there are four types of acute idiopathic autonomic neuropathy, classified according to somatic nerve involvement: acute pandysautonomia, which has minimal or no motor or sensory dysfunctions[3];acute autonomic and sensory neuropathy in which sensation is seriously involved[4–6]; Guillain-Barré syndrome with prominent dysautonomia, manifesting autonomic and somatic motor dysfunctions; and acute autonomic sensory and motor neuropathy, characterised by prominent dysautonomia and severe motor and sensory impairment. Despite minimal or no sensory disturbance, reduction of myelinated fibres in biopsied sural nerve has been found in several cases with acute pandysautonomia.[3] However, the exact site of pathological involvement in the sensory system remains unknown, because postmortem examinations have seldom been performed. We report a case of acute pandysautonomia with no evidence of significant somatic nerve involvement, accompanied by dorsal root ganglionopathy shown by postmortem examinations.

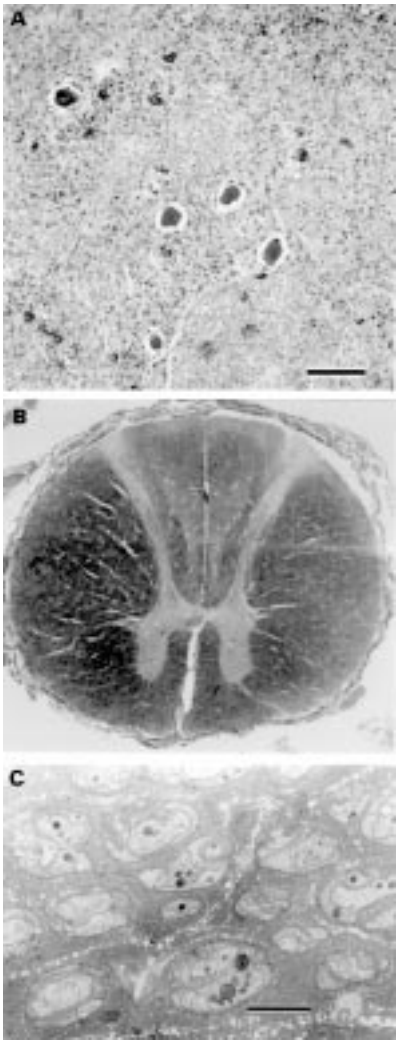
An 18 year old male student experienced low grade fever, vomiting, and tingling pain in the limbs on 26 February 1987. Orthostatic syncopy occurred three times on the next day. Difficulty in emptying the bladder, alternate diarrhoea and constipation, and lack of sweating over the whole body developed rapidly. He was admitted to the Third Department of Internal Medicine, Medical College of Oita on 24 April 1987. On physical examination, he weighed 46 kg, with a recent weight loss of 14 kg. Blood pressure was 108/78 mm Hg in the supine position and heart rate was 88/min. When changing from the supine to theupright position, he lost consciousness and blood pressure became unmeasurable. On neurological examination, he had emotional instability. Both pupils were midsized, irregular, and reacted sluggishly to light. Jaw jerk was slightly exaggerated and deep tendon reflexes of the limbs were diminished. No obvious muscle weakness was found. Touch sensation and deep sensation were normal, but dysaesthesia and hypalgesia on his face and the upper part of the level of Th4, and slight hypalgesia of the limbs were found. The clinical manifestations of autonomic failure were orthostatic hypotension, lack of sweating, alternative diarrhoea and constipation, and impotence.

There were no abnormal findings in laboratory examination of blood and urine. Cell count in the CSF was normal, but protein concentration was slightly high at 54 mg/dl. Head CT and EEG were normal. Nerve conduction studies and EMG showed no abnormalities. Right sural nerve biopsy showed a marked loss of small myelinated and unmyelinated fibres. There were some myelin ovoids in teased fibres. The hand grip test and the cold pressure test showed no rise in blood pressure. There was no overshoot in the Valsalva manoeuvre. Serum noradrenalin concentration decreased to 110 pg/ml (normal 145–575 pg/ml) at rest, and failed to respond to tilting. A noradrenalin infusion test (0.01~0.04 μg/kg/min) showed an excessive increase in blood pressure, from 90/58 to 120/78 mm Hg. The R-R interval variation was 4.55% at rest (normal 3%–6%). During aocular pressure test the patient had a normal bradycardic response. The instillation of 1.25% adrenaline into the conjunctival sac of the eye produced 37.5% dilatation of the pupil (normal <25%). Five per cent cocaine and 5% tyramine produced 12.5% and 28.6% dilatation respectively (normal; >30%). Addition of 2.5% methacholine resulted in a 12.5% reduction in pupillary size (normal <25%). Sympathetic skin responses were not evoked. Amezinium metilsulphate, an indirect sympathomimetic agent, was effective on orthostatic hypotension and coughing attacks. In April 1992, the patient fractured both legs in a traffic accident and was admitted to the Department of Orthopedics in Hiroshima University Hospital. On admission, he still complained of dizziness on standing, defective sweating, urinary bladder symptoms, and impotence. No sensory symptoms and signs were found. Nerve conduction studies were normal. The leg fractures were difficult to heal, and he underwent orthopaedic surgery several times. Although nerve conduction studies again disclosed no abnormality, he developed severe pneumonia and died of respiratory failure at the age of 25 in 1994.

On necropsy 10 hours after death, the brain weighed 1440 g, and no tumour was found in any part. The most prominent finding was located in the lumbar (L5) dorsal root ganglia . There was a marked reduction in the number of ganglionic neurons, whereas clusters of satellite cells were easily seen (figure A). The dorsal columns of the spinal cord showed a loss of myelinated fibres (figure B). No other detectable changes were present in the CNS including the brainstem, the intermediolateral nucleus of the thoracic spinal cord, and Onuf's nucleus. The celiac ganglia showed no abnormalities, but the sympathetic trunk was not examined. Lymphocytic infiltrates with perivascular distribution were not found anywhere in the nervous system. Electron microscopic examinations of the left distal sural nerve showed profound changes with a remarkable reduction in both myelinated and unmyelinated fibres, which decreased to 1236, and 4560/mm^2 /unit respectively. The size/frequency histogram of myelinated fibres showed a reduction in both large and small fibres. The histogram of axons devoid of myelin showed a monomodal curve with a peak situated at about 1.2 μm. Numerous budded Schwann cell bands were found (figure C), often associated with cells surrounded by additional layers of basement membrane. Myelin sheath irregularities were occasionally encountered. Regenerative alterations such as growth cones, clusters of small myelinated axons, and onion bulb formations were rarely seen.

The patient rapidly developed severe autonomic failure with only mild sensory nerve involvement manifested by dysesthesia and hypalgesia. Orthostatic hypotension and diminished sweating indicated sympathetic failure. Parasympathetic failure was assumed from alternate diarrhoea and constipation, bladder paresis, and penile impotence. Abnormally decreased serum concentration of noradrenaline that remained low during tilting, and excessive increase in blood pressure by low concentration noradrenalin infusion suggested that the main lesion was located in the postganglionic fibres of the sympathetic system. This notion was consistent with the profound loss of unmyelinated fibres in the sural nerve. As no pathological alterations were found in the CNS except for the posterior columns of the spinal cord, we diagnosed this case as acute idiopathic autonomic neuropathy, based on the associated somatic sensory and motor neuropathy. The present case could be clinically regarded as acute pandysautonomia, as the patient's sensory symptom was mild and short lasting and because no abnormalities were found in nerve conduction studies.

The site of pathological involvement of the sensory system in patients with acute pandysautonomia has not been clarified. Our patient, as those in previous reports[3], had a loss of myelinated fibres on sural nerve biopsy. Also, we found that the dorsal root ganglia showed a loss of ganglionic neurons and clusters of satellite cells. Only a few cases



(A) Loss of ganglionic neurons with clusters of satellite cells in the dorsal root ganglion. (Haematoxylin and eosin stain, bar = 100 μm.) (B) Loss of myelin staining in the dorsal columns of the thoracic spinal cord. (Luxol fast blue / Nissl stain). (C) Numerous budded Schwann cell bands in the sural nerve (bar = 2 μm).

of acute idiopathic autonomic neuropathy have been verified by necropsy[4–6]. Fagius *et al*[4] and Tohgi *et al*[5] found a marked loss of myelinated nerve fibres in the dorsal column, dorsal root, and peripheral nerve. Disappearance of nerve cell bodies replaced by clusters of satellite cells in the dorsal root ganglia was found in the patient of Fagius *et al*.[4] Stoll *et al*[6] also found symmetric degeneration of the dorsal columns with severe ganglionitis of both the sensory and autonomic ganglia. However, their patients showed a marked sensory disturbance with no evoked sensory nerve action potentials, as well as motor nerve involvement of a greater or lesser degree. Therefore, these cases could be classified as acute autonomic and sensory neuropathy or acute autonomic and sensory and motor neuropathy. Also, the patient of Fagius *et al*[4] had an associated malignant tumour in the testis that recurred during the course of pandysautonomia. Neuropathological examination disclosed CNS involvement manifested by degeneration in the preganglionic autonomic nervous system in the case of Tohgi *et al*[5], and a mild chronic encephalomyelitis with perivascular lymphocytic infiltrates in the patient of Stoll *et al*.[6] The present case could be the first that showed sensory ganglionopathy associated with acute pandysautonomia.

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Premenstrual exacerbations of multiple sclerosis

Although relapses of multiple sclerosis occur unpredictably and at odd intervals, two factors have been identified that may trigger an exacerbation: viral infections and the puerperium.[1 2] Viral infections probably act through a release of inflammatory cytokines, such as interferon-γ (INF-γ), that stimulate the immune system and facilitate the entry of activated T lymphocytes into the CNS.[1] Relapses during the puerperium are likely to be precipitated by changes in the hormonal milieu after delivery.[2] We report on three patients with multiple sclerosis in whom successive exacerbations occurred exclusively during the premenstrual period.

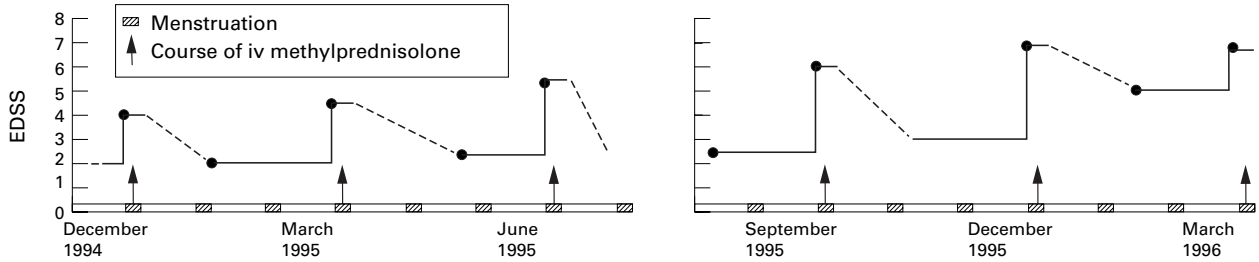
Patient 1, a 21 year old women student sought evaluation for episodes of alternating right and left sided paraesthesias, which existed for about 4 months. She also complained of fatigue. There was a history of infectious mononucleosis 6 years earlier. She did not use an oral contraceptive. Neurological examination showed hyperreflexia and Babinski's sign in the right leg. Magnetic resonance imaging of the brain showed multiple white matter lesions on T2 weighted sequences, mainly in the left occipital and right parietal lobe. Oligoclonal bands were present in the CSF. One month later she was admitted to hospital because of weakness in the left leg, urge incontinence, and diminished sensation below Th7. Symptoms had started 3 days before her menstruation. She was treated with 1 g/day intravenous methylprednisolone for 5 days with rapid improvement over the next 2 weeks.

One month later she presented with a left hemiparesis and diminished sensation below Th1, which had started 2 days before the menstruation. She was treated with high dose intravenous methylprednisolone. During the next premenstrual period, 1 day before onset of the menstrual bleeding, she developed right sided cerebellar ataxia and diminished vision in the left eye; the expanded disability status scale (EDSS) was 5.0. She received a course of high dose intravenous methylprednisolone. Two months later the EDSS was 2.5, and she was included in an open pilot study with bromocriptine. Her clinical state did not change until 11 months later when she presented with worsening of right sided cerebellar ataxia; the symptoms had started 2 days before the menstruation. The ataxia improved gradually without corticosteroid treatment. After completion of the 1 year period specified in the trial protocol, she continued bromocriptine for another 8 months, and then stopped. She had no relapses on follow up for >3 years. At the last visit her EDSS was 2.0.

Patient 2 gave birth to two boys after uncomplicated pregnancies at the ages of 21 and 26. She used an oral contraceptive between the ages of 28 and 31. At the age of 33, 2 days before her menstruation, she noticed weakness in the right leg. This improved gradually over the next 3 weeks. Six months later, on the day before her menstruation, she developed a right sided hemiparesis. Brain MRI showed widespread white matter lesions of high intensity signals on T2 weighted sequences. Visual evoked responses were delayed. Examination of CSF showed oligoclonal bands. She was treated with high dose intravenous methylprednisolone, which was followed by gradual improvement. Three months later she experienced left sided facial weakness and coordination disturbances, and subsequently with intervals of about 3 months, she had three further relapses. Each relapse occurred during the premenstrual period (1 to 4 days before menstruation), and was treated with a course of high dose intravenous methylprednisolone. During the next 2 years her condition was stable; at the last visit her EDSS was 2.5.

Patient 3 was a 33 year old nulliparous woman in previous good health who experienced numbness in the right side of her body. She did not use an oral contraceptive. On examination there was diminution of touch, pinprick, and proprioceptive sensation over the right side of the body. The tendon reflexes on the right side were brisker, and a right Babinski's sign was present. Brain MRI showed multiple hyperintense white matter lesions in the periventricular areas, cerebellum, and pons on T2 weighted sequences. Examination of CSF showed oligoclonal bands. In December 1994 she was admitted to hospital because of weakness in the right arm and numbness in the left arm and leg. Symptoms had started 2 days before onset of menstruation. She was treated with high dose intravenous methylprednisolone, resulting in gradual improvement. Between December 1994 and March 1996 she had 5 further relapses, occurring with intervals of 3 months. All relapses started 1–4 days before menstruation, and were treated with a course of high dose intravenous methylprednisolone (figure). After exacerbation in March 1996 she was treated with subcutaneous INF-β-1b and she started a vegetarian diet. There were no further relapses up to her last visit in July 1997.

These 3 women with relapsing-remitting multiple sclerosis had a particular disease course, characterised by exacerbations that occurred exclusively during the premenstrual period. This is probably different from the premenstrual transient worsening of existing symptoms which occurs in many women with relapsing-remitting multiple sclerosis.[3] However, we cannot exclude that the underlying mechanism is different and that the patients described here may be at one end of a range. Exacerbations in the premenstrual period are likely to be triggered by dynamic changes in sex hormone concentrations. Before the



Relation between changes in EDSS and the menstrual cycle in patient 3.