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Letters

Severe peripheral neuropathy due to lithium intoxication

Sir: Central nervous system damage due to lithium intoxication is well known,[1] but evidence of peripheral nervous system damage is scanty. Three reports of individual cases have been made;[1-3] in only one was the neuropathy severe, and all three cases recovered without apparent sequelae. We report a case of severe, persisting central and peripheral nervous system damage following lithium intoxication.

A 31-year-old man with a history of manic-depressive psychosis had been maintained on lithium carbonate 1500 mg/day. While working as a volunteer on an Israeli kibbutz, the dose was inadvertently increased to 1800 mg/day. He was admitted to a local hospital after the gradual onset of confusion, weakness, and tremulousness. Serum lithium level on admission was 3·63 mmol/l, and daily haemodialysis was instituted. However, he became comatose after two days and required assisted ventilation. Nephrogenic diabetes insipidis was diagnosed and treated with frusemide and salt restriction. He regained consciousness 11 days after admission, but could obey only simple commands, was hardly able to speak, could swallow liquids only, and remained bedridden. Urinary tract infections were treated with carbenicillin and amikicin. Diarrhoea was treated with diphenoxylate and atropine. Serum lithium by the 18th hospital day had fallen to 0·34 mmol/l, and 8 weeks after admission he was transferred back to Australia. Examination revealed a wasted bedridden young man who was mute. He could obey very simple verbal commands, but any attempt to elicit speech or complex motor tasks caused extreme agitation accompanied by grinding of his teeth. Snout, sucking and bilateral grasp reflexes were elicited. Gag reflex was absent and he was unable to swallow. Upper limb movements were accompanied by gross intention tremor; there was marked hypotonia and distal muscle weakness, with complete left wrist drop. There was flaccid paralysis of the lower limbs and extensive decubitus ulceration. Deep tendon reflexes were diminished proximally and absent distally in arms and legs. Both pinprick and joint position perception were absent distally in all limbs. Haemoglobin was 11·4 g/dl, white blood count $15{\cdot}7 \times 10^9$, serum albumin 32 g/l, potassium 2·5 mmol/l. Other routine haematological and biochemical tests were normal. The cerebrospinal fluid contained no cells, but the protein level was elevated at 0·70 g/l. Serum B12, urinary heavy metals, and porphyrin studies were normal. An electroencephalogram showed diffuse theta and occasional delta waves. Computed tomography of the head showed a mild degree of cerebral atrophy. Nerve conduction studies confirmed the presence of a severe peripheral neuropathy: no sensory or motor responses could be obtained in the lower limbs, while in the upper limbs the amplitude of both sensory action potentials and compound muscle potentials was reduced. However, motor conduction velocity of both median and ulnar nerves was normal. Right sural nerve biopsy revealed moderate loss of myelinated fibres. Many fibres showed evidence of axonal degeneration: there was splitting of myelin lamellae, myelin breakdown products within macrophages, dense body accumulation within axons, and marked enlargement of the endoneurial space. Biopsy material was also examined with the teased fibre technique and under the electron microscope, and these examinations confirmed acute axonal degeneration. Twelve months later he could walk in a frame with the aid of two people. He remained weak distally with absent distal tendon reflexes, but his speech and tremor had improved.

This patient showed many of the central nervous system effects of lithium intoxication. In addition he had a severe persistent peripheral neuropathy, which was shown to be due to acute axonal degeneration. Other known causes of this type of peripheral neuropathy were excluded by history or special investigations. Abnormal nerve conduction velocities have been recorded in manic-depressives and asymptomatic volunteers receiving lithium.[4] It is becoming increasingly apparent that lithium intoxication can cause a peripheral neuropathy of varying severity. A mild neuropathy could be overlooked as the central nervous system damage is usually more dramatic. A peripheral neuropathy should be looked for in all patients on chronic lithium therapy, and may be more common and potentially more serious than previously thought.

We thank Associate Professor John Pollard, University of Sydney, who prepared and examined the nerve biopsy.

ROGER S PAMPHLETT
RODERICK A MACKENZIE
Dept of Neurology,
Concord Hospital,
Hospital Rd, Concord 2139,
New South Wales, Australia

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Acute autonomic and sensory neuropathy associated with elevated Epstein-Barr virus antibody titre

Sir: We report a rare case with neuropathy manifesting marked autonomic and sensory disturbances associated with high antibody titres of Epstein-Barr virus. On 9 March 1978, a 23-year-old Japanese woman noticed pricking sensation and paraesthesiae of the whole body. Muscle weakness of all extremities occurred rapidly and two days later she became bedridden. She had dysarthria, dysphagia, nausea, vomiting and hypersalivation. On the fourth day of illness, she experienced difficulty in respiration and urinary retention. Two months later, dysarthria, dysphagia, and muscle weakness gradually improved. She became able to walk 9 months after the onset, when she began to experience fainting spells upon arising. In spite of noticeable improvement of muscle power, severe sensory impairment of the whole body and diarrhoea persisted. She often burned her hand when cooking. The patient was transferred to our hospital 2 years and 8 months after the onset. There was no history of intoxication by drugs or food preceding the illness. Past history, family history and life history were noncontributory.

Physical examination on admission revealed marked emaciation, anhidrosis, corneal erosion, diminished lacrimation and salivation, burn scars on the forearms and diminished bowel sounds. Her blood pressure was 134/90 mmHg when supine and 60/0 mmHg when standing without increase in heart rate. Neurologically the right pupil was oval-shaped and 3·5 mm in diameter, the left was round and 3·0 mm. Light reflex was sluggish but convergence reflex was prompt bilaterally. The corneal reflex was absent. Muscle power was mildly weak in the distal upper extremities. Deep reflexes were absent. Romberg's sign was positive and gait was ataxic. Sensation was lost to all modalities in the whole body except for a segmental sparing in the right shoulder and in the circumference of the lower abdomen. There was no sphincter disturbance. The following laboratory findings showed normal values: CBC, urinalysis, ESR, serological tests for syphilis, liver function tests, serum electrolytes, blood urea nitrogen, creatinine, CRP, antinucleic factor, LE-test, glucose tolerance test, urinary 24-hours excretion of catecholamine, homovanillic acid, vanillylmanderic acid and porphobilinogen, plasma dopamine-beta-hydroxylase activity, thyroid function, LH, FSH, GH and cortisol. Chest radiograph, electrocardiogram, electroencephalogram, brain CT scan and upper gastrointestinal studies were normal. Paul-Bunnel test was normal, but Epstein-Barr virus (EBV) antibody titres were elevated in the serum (EBV·VCA-IgG × 1280, EB-EBNA × 160, EBV·VCA-IgM × 40, EBV·EA-DR·IgG <× 10). Cerebrospinal fluid was normal on the third day of the illness and also 2 years and 9 months later. Oligoclonal IgG band was negative. Motor nerve conduction velocities were normal. Sensory nerve conduction studies revealed no response in the median and sural nerves. Electromyogram was normal. The biopsied sural nerve revealed severe loss of myelinated and unmyelinated fibres. There was no inflammatory response or abnormal deposits (figure). No leprous organelles were seen in the biopsied skin and nerve, or on nasal septum smears with Ziehl-Neelsen staining. The table shows the autonomic nervous function of the patient, revealing postganglionic dysfunctions in both sympathetic and parasympathetic system.

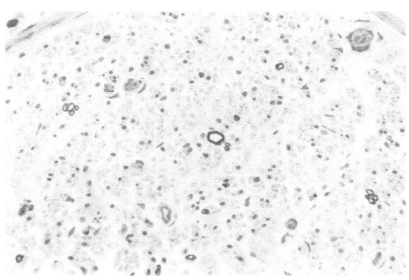

Figure *Biopsy of sural nerve shows severe loss of myelinated fibres. Toluidine blue. × 100*

Table *Results of autonomic nervous function tests*

Tests	*Responses*
5% cocaine ophthalmic instillation	No pupillary response
5% thyramine ophthalmic instillation	No pupillary response
1·25% epinephrine ophthalmic instillation	Marked mydriasis
Ephedrine (25 mg) im injection	No increase in blood pressure
Epinephrine (0·25 mg) subcutaneous injection	Hypersensitive in blood pressure
Acetylcholine intradermal injection	No piloerection
Valsalva's manoeuvre	No overshoot
Cold pressor test	No increase in blood pressure
Thermal sweating test	Anhidrosis
Postural hypotension	Severe with syncope
2·5% methacholine ophthalmic instillation	Marked miosis
Atropine (1·0 mg) iv injection	No increase in heart rate
Gastric acidity (insulin load)	No increase in acidity
Carotid sinus massage	No change in heart rate
Shirmer test	Decreased lacrimation
Saliva flow test	Decreased salivation

The present case is a unique neuropathy with acute onset of sensory, autonomic and motor disturbances without obvious prodromes, being characterised by poor recovery of sensory and autonomic disturbances in contrast with good improvement of motor dysfunction. Diabetic neuropathy, carcinomatous neuropathy, leprous neuropathy, toxic neuropathies including botulism, and the Riley-Day syndrome are unlikely. Guillain-Barré syndrome is also unlikely because of segmental distribution of sensory disturbance, severe dysautonomia, normal cerebrospinal fluid and no demyelination in the sural nerve. Since 1969, there have been 10 reported cases with "pure pandysautonomia".[1-9] This occurs acutely with the symptoms limited to the autonomic nervous system and with normal cerebrospinal fluid, normal histopathological findings in peripheral nerves and complete recovery. The present case showed not only dysautonomia, but also sensory and motor disturbances with marked pathological changes in peripheral nerve and poor recovery. Therefore, this case must be differentiated from "pure pandysautonomia". In 1980, Colan *et al*[10] reported a 9-year-old boy with "acute autonomic and sensory neuropathy", manifesting severe sensory impairment and postganglionic dysautonomia with marked loss of myelinated and unmyelinated fibres. In their case sensory disturbance remained but autonomic dysfunction improved. The present case also showed the postganglionic dysautonomia and severe nerve fibre loss, and it is, therefore, very similar to their case. They attributed the main lesion to the sensory and autonomic ganglionopathy of unknown cause.

It is noteworthy that EB virus antibody titres were elevated in the present case, which were examined 2 years and 9 months after the onset. In contrast with the normal titre value of IgM antibody against EBV-viral capsid antigen (EBV·VCA-IgM) and antibody to EBV early antigen (EBV·EA-DR·IgG), which usually rise early and transiently in an acute disease process, titres of IgG antibody against EBV-viral capsid antigen (EBV·VCA-IgG) and antibody to EBV nuclear antigen (EB-EBNA) were elevated. This suggests that the patient was severely infected with EBV formerly. According to Silverstein *et al*[11] any neurological abnormality may occur in EB virus infection. Two cases of dysatonomia,[7,9] which were preceded by infectious mononucleosis and ascertained immunoserologically to have an infection with EBV, have so far been reported. Price and Notkins[12] pointed out that the autonomic dysfunction could be produced by a virus infection of the autonomic nervous system, especially of the autonomic ganglia. Therefore it is reasonable in the present case to suppose that EB virus infection played a role in the disease process and that the lesions were situated in sensory and autonomic ganglia.

NAOKI FUJII*
TAKESHI TABIRA*
HIROSHI SHIBASAKI*
YOSHIGOROU KUROIWA*
AKIO OHNISHI†
JOJI NAGAKI‡
**Department of Neurology, Neurological*

Institute, Kyushu University 60, Fukuoka 812, Japan
†Department of Neuropathology, Neurological Institute, Kyushu University 60, Fukuoka 812, Japan
‡Minamata Kyoritsu Hospital, Sakuraicho 2-2-12, Minamata City, Kumamoto prefecture 867, Japan

Address for reprint requests: Dr N Fujii, Department of Neurology, Neurological Institute, Kyushu University 60, Fukuoka 812, Japan.

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Multiple sclerosis in association with dialysis encephalopathy syndrome

Sir: Since its first description in 1972, the syndrome of dialysis encephalopathy has occurred in numerous centres in the United States, Europe, and Australia.[1 2] This condition is characterised by speech and language changes and seizures. A typical electroencephalographic abnormality precedes the clinical symptoms by six to eight months, continuing throughout the illness. In nearly every instance, the course of the disease is inexorable, resulting in death in less than a year. The pathogenesis of this condition, in spite of several theories, has not been elucidated. We have observed a patient with a typical dialysis encephalopathy, who also developed multiple sclerosis, suggesting that immunological features of dialysis encephalopathy do not preclude the development of the demyelinating illness. To our knowledge this association has not been previously recorded.

A 37-year-old white female was admitted to the Brigham and Women's Hospital with a speech and gait disorder of several months' duration. She had been on home dialysis for ten years, for the most part using untreated tap water. Renal biopsy had shown chronic glomerulonephritis. She had had rheumatic valvular disease with an aortic-valve replacement following staphylococcal endocarditis. Medications upon admission included coumarin and an aluminium-containing oral antacid. On admission the patient was disoriented and inattentive, and both recent and remote memory were impaired. Speech was dysmelodic and was punctuated by frequent arrests, as well as by numerous literal paraphasias. Comprehension and repetition were relatively spared. She had poor penmanship with frequent spelling errors although she sometimes preferred to communicate in the written mode. Her drawings and constructions were impaired. The cranial nerves were normal. She was generally wasted with increased tone, hyperreflexia and extensor plantar responses. Both lower limbs were weak, the right slightly more than the left. She had a spastic gait with inversion of the right foot on walking. Sensory examination was unreliable, but it appeared that there was a sensory loss over the right lower trunk and upper thigh. Routine laboratory values were unremarkable. She had a serum aluminium of 31, normal being less than 50 mEq per 100 ml. Lumbar puncture revealed spinal fluid with a glucose of 62 mg per 100 ml, a protein of 22 mg per 100 ml, and a gamma globulin of 3·8 mg per 100 ml. A CT scan showed evidence of mild cerebral atrophy. A myelogram was normal. An EEG revealed bursts of high-voltage delta waves occurring anteriorly with intermittent spikes and sharp waves. Visual evoked potentials were abnormal (right eye 145 ms, left eye 117 ms, normal 108 ms or less). Somatosensory evoked potentials could not be satisfactorily recorded.

Despite an initial favorable response on EEG and clinical testing to diazepam and later to clonazepam, she had a progressive downward course. Weakness, hyperreflexia, pseudobulbar signs, painful flexor spasms, facial and limb myoclonus, seizure activity, progressive dementia, and speech difficulty all developed. Valproic acid, phenobarbitone, and phenytoin, as well as intravenous ACTH, had no effect. She died three months after admission. At necropsy the patient's kidneys showed end-stage renal disease with cystic degeneration. On gross external inspection the brain showed mild frontal atrophy. Serial coronal sectioning of the cerebral hemispheres revealed scattered, irregular, sharply defined small zones of gliosis and myelin loss. These were present about the lateral and third ventricles and in the white matter of the centrum semiovale. Serial *en bloc* horizontal sections of the brainstem and cerebellum revealed occasional similar lesions in the white matter of the brainstem. Histological examination of these lesions showed them to be demyelinated plaques of multiple sclerosis. Some were active, other quiescent. The active lesions showed a lymphocytic-macrophage infiltrate at the advancing edge. The older lesions contained only rare mononuclear cells and were gliotic.

The syndrome of chronic dialysis encephalopathy has a fairly consistent clinical picture. In the majority of patients, there is a speech and language disorder characterised by a halting, hesitant dysarthria with frequent speech arrests, literal and phonemic paraphasias, and relatively preserved comprehension. The speech disorder may vary according to the dialysis schedule; worsening during and after dialysis. Multifocal myoclonic movements are seen involving the limbs and face, with seizures appearing later in the course of the illness. Various psychiatric symptoms may appear, all against a background of progressing dementia. Electroencephalographic changes occur early in the illness, appearing as bursts of high-voltage delta waves predominantly anteriorly with random sharp spikes and triphasic waves with a relatively normal background.[3] This EEG and set of clinical symptoms have been shown to respond initially to diazepam or clonazepam or both;[4] however, in all but a few instances, the clinical course is inexorable, with death occurring in 1 to 15 months after the onset of the illness.[1 2] A body of evidence has accumulated, linking