proposed in stiff man syndrome, in which anti-GAD antibodies are typically seen in about 60% of patients.³ However, patients with stiff limb syndrome seem to have different neurophysiological abnormalities from stiff man syndrome² and fewer of these patients have anti-GAD antibodies; they also typically show a poorly sustained response to baclofen and diazepam. The response to immunotherapy in stiff limb syndrome is not known, whereas patients with stiff man syndrome may respond to intravenous immunoglobulin^{4,5} as well as possibly plasma exchange.⁶⁻⁸ We now report on a patient with stiff limb syndrome who responded dramatically to plasma exchange and in whom an anti-axonal antibody was isolated, suggesting that this condition may have an immunological basis.

A 50 year old retired auxiliary nurse presented with a 10 year history of progressive pain, stiffness, and flexion contractures in her hands, followed by increasing immobility. Her neurological problems began at 24 years of age when she developed viral meningitis based on a headache, fever, and a CSF lymphocytosis, that resolved after a week. At the age of 28 she complained of back and leg pain with urinary retention but displayed no abnormal neurological signs and had a myelogram that was normal. Her leg symptoms resolved, but she continued to complain of urinary retention and frequency, for which no cause was found. She went on to have a urethrotomy which did not relieve her symptoms. At the age of 40 she started to develop stiffness and pain in the hands, which slowly clawed, after which her arms and neck became progressively stiffer and her trunk became increasingly stooped on walking, with additional difficulty raising her arms above her head. Five years after the onset of her symptoms she was incapacitated, required assistance with all activities of daily living, and was permanently catheterised. At this stage a seronegative polyarthritis was diagnosed and she was treated with hydroxychloroquine, prothiaden, and corticosteroids, all without effect. She subsequently had some spontaneous remission but at the time of her referral to us she could only walk 10 yards with one stick and continued to complain of heaviness, pain, and stiffness in the limbs especially the left arm. In addition she had developed an intermittent tremor of the right arm and leg, which sometimes affected her jaw and she had difficulty swallowing large boluses of food.

Examination at this time showed her to have flexion contractures of all fingers. She had irregular jerking movements of her right arm and leg that were accentuated by moving the limb or walking a few steps. She had difficulty standing up from a chair without assistance and although she was not weak on formal examination, all limb movements were accompanied by pain. No reflex or sensory abnormalities were found and her plantar responses were flexor.

Investigations showed normal nerve conduction studies as well as a normal CSF examination including negative oligoclonal bands; brain and spine MRI, and routine haematological and biochemical tests were also normal. Her autoantibody screen was negative as were her anti-GAD and anti-neuronal antibodies although an anti-axonal antibody was detected in her serum which is currently being further characterised. More extensive neurophysiology showed her to have an abnormal hypersegmented EMG pattern

during muscle spasms although no continuous motor unit activity was recorded at rest. The latency of responses to magnetic stimulation of the motor cortex was normal.

The diagnosis of stiff limb syndrome was made and she was initially treated with diazepam and baclofen, but continued to deteriorate and gradually lost all useful function of her arms. There was a similar lack of response to intravenous methylprednisolone, so she was given intravenous immunoglobulin, to which she developed an anaphylactic reaction. Her disorder progressed and she developed prominent rigidity and spasms of the face, trunk and limbs. Her speech developed a strangled quality and she had episodes of involuntary tachypnoea apparently due to spasm of respiratory muscles. She was bed bound and totally dependent for all activities of daily living, needing constant nursing. As a result it was decided to give her empirical treatment with two courses of plasma exchange in November and December 1996. After the first exchange, the spasms of her facial and respiratory muscles ceased and after the second there was a slow sustained improvement in limb power, so that after 6 months she had regained independence. For the next 18 months she walked and lived normally, even travelling on holiday. This improvement was punctuated by two admissions with chest infections and impaired respiratory function, which responded well to antibiotics.

Unfortunately the stiffness and tremor of her limbs returned in June 1998 and by November of that year, she was once again immobile and dependent such that she could barely wash herself and was unable to walk at all. Any attempt to move her limbs caused disabling tremor and stiffness. Again, reflexes and plantars were normal. She had a further course of plasma exchange and again responded slowly, such that 3 months later she was able to walk on two sticks. This improvement was initially sustained although she has required a further course of plasma exchange in February 2000 and has now been started on oral cyclophosphamide with notable benefit. The patient has not had further neurophysiological investigations.

This case has all the features of stiff limb syndrome with the novel finding of anti-axonal antibodies detected in the serum. The patient failed to respond to baclofen and diazepam and could not tolerate intravenous immunoglobulin but did have a dramatic and sustained response to plasma exchange, although the need for repeated courses of this treatment has led to her being started on cyclophosphamide. This has not been reported before for this condition and whereas this case illustrates the possible therapeutic effect of this treatment, it also raises the possibility that stiff limb syndrome may have an immunological basis.

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Acute autonomic and sensory neuropathy after interferon α -2b therapy for chronic hepatitis C

Acute autonomic and sensory neuropathy (AASN) is a disorder characterised by acute autonomic and sensory nerve dysfunctions, and well preserved motor nerve function.¹ Although the pathomechanism of AASN is not clear, autonomic and sensory ganglion neuron cell bodies may be the main target of the immune mediated process underlying AASN.² On the other hand, patients treated with interferon may develop neurological complications including neuropathy.³ We report the first case of AASN which can be associated with interferon α -2b therapy for chronic hepatitis C.

A 57 year old Japanese man with chronic hepatitis C had been treated with interferon α -2b since June 1998. On 3 September, a skin eruption abruptly emerged on his chest and rapidly spread over his whole body. There was no history of exposure to toxins and drugs other than the interferon. The interferon therapy was stopped on 7 September; after a total dose of 390 000 000 units. The skin eruption gradually resolved, but 1 week later, numbness appeared in his limbs. Subsequently he became unable to walk and stand. Further, he developed urinary overflow incontinence and bowel distension. He was then transferred to our neurology department on 2 October.

Physical examination disclosed orthostatic hypotension without secondary tachycardia (120/60 mm Hg lying, 85/52 mm Hg sitting, fixed pulse rate 60 bpm) and paralytic ileus. He was catheterised for incontinence. He was drowsy. The pupils were anisocoric although they reacted promptly to light. Other cranial nerves were unremarkable. Muscle strength and bulk were normal. Deep tendon reflexes were generally absent. There were no pathological reflexes. Light touch, pain, and temperature sensations were impaired moderately over the trunk, more so in his limbs. Vibration and joint sensations were impaired severely in the same distribution, and lost in

his fingers, knees, ankles, and toes. Sensory ataxia and pseudoathetosis in his fingers were noted.

Routine laboratory examinations were normal except for hyponatraemia due to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (plasma sodium 124 mEq/l, urinary sodium 182 mEq/l, plasma osmolality 262 mOsmol/l, urine osmolality 775 mOsmol/l, vasopressin 1.86 pg/ml; and normal renal, thyroid, and adrenal function). Liver function was normal, and blood hepatitis C virus RNA was negative. Immunoglobulins and complements were normal. Cryoglobulin, M-protein, antinuclear antibody, and anti-SS-A/-B antibodies were negative. We examined various antiviral antibodies (coxsackie viruses, herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, measles, rubella, mumps, adenovirus, and influenza A and B) in the serum or CSF, but they showed no remarkable change. Several tumour markers in the serum also showed no particular change. Serum IgG

class anti-GQ1b antibody was present with low titre as demonstrated by enzyme linked immunosorbent assay (ELISA). Immunohistochemistry using frozen sections of rat cerebral cortex, cerebellum, spinal cord, and dorsal root ganglion showed no antineuronal antibody in the serum from the patient, although the serum from a patient with anti-Hu antibody positive paraneoplastic syndrome showed positive reactions with these neurons (data not shown). ELISA for anti-Hu antibody was negative in the serum and CSF. His CSF showed an increased protein concentration (159 mg/dl) without pleocytosis but no oligoclonal bands.

Brain and spinal MRI were normal. Whole body CT examination; colon fibroscopy and a ^{67}Ga -citrate scintigram showed no malignancy.

On neurophysiological studies, an EEG showed delta bursts in all leads. Motor conduction velocity and amplitude of compound muscle action potentials in the right median, ulnar, and posterior tibial nerves

were within the normal range. By contrast, sensory nerve action potentials (SNAPs) could not be elicited in right median and sural nerves. In the right ulnar nerve, amplitude of SNAPs was markedly decreased (5 μV) with preservation of sensory conduction velocity (53.3 m/s). A needle EMG gave normal results. Sympathetic skin response could not be elicited in the upper and lower limbs. The coefficient of variation of R-R intervals on ECG was decreased (1.17% at rest; mean value and lower limit in the 50s age group 2.80, 1.41).

The sural nerve biopsy disclosed marked axonal degeneration with a significant decrease of both myelinated (1359/mm²) and unmyelinated fibres (13 791/mm²) (figure). There was no inflammatory cell infiltration or vasculitis.

The patient was treated with plasmapheresis (3000 ml $\times$ 3) beginning on 6 October. Soon after the plasmapheresis, joint sensation in his fingers was slightly improved and anisocoria disappeared. Plasma sodium concentration, the patient's level of consciousness, and the EEG were subsequently normalised. After the plasmapheresis, he was treated with steroids (methylprednisolone (1000 mg intravenously), for the first 3 days, and then prednisone (60 mg orally), followed by a gradual taper). This did not further improve his symptoms; severe sensory impairment, orthostatic hypotension, and constipation persisted 3 months after the onset of the disorder.

Our patient presented with acute onset of sensory impairment, autonomic dysfunctions, selective impairment of sensory and autonomic nerves in electrophysiological studies, and a raised CSF protein concentration. These clinical features are compatible with a diagnosis of AASN. In addition, our patient showed SIADH and consciousness disturbance suggestive of involvement of the CNS.⁴

In AASN, episodes of infection before the onset are often seen, suggesting that preceding infection may induce the immune mediated process leading to AASN. Pavesi *et al* described a patient with Coxsackie B virus infection complicated by an acute autonomic and sensory neuropathy.⁵ In their patient, diffuse mucosal and cutaneous erythema preceded neurological complications. Our patient also presented a cutaneous lesion followed by an autonomic and sensory neuropathy. However, serum and CSF studies for antiviral antibodies showed no evidence for any viral infection.

Peripheral neuropathy is a rare neurological side effect of interferon. There have been reports of multiple mononeuropathy, acute motor or sensorimotor axonal polyneuropathy, and cranial nerve palsies. Although the pathomechanism underlying peripheral neuropathy associated with interferon is unknown, immunomodulatory effects of interferon may cause disorders of the peripheral nervous system.³

In our patient, AASN developed after the interferon therapy with an increased protein concentration in the CSF, and plasmapheresis seemed to result in slight improvement and prevention of the disease progression. This is the first report suggesting association of interferon and AASN. We suggest that interferon may induce an immune mediated

Pathological findings in the sural nerve. (A) Histologically, most of the myelinated fibres show formation of myelin ovoids indicating active axonal degeneration, which is also present in the teased fibre preparations (B). (C) The unmyelinated fibres are also affected showing swelling of the axons (arrows). ((A) epon embedded section stained with toluidine blue; bar=20 μm ; (B) teased fibre, bar=100 μm ; (C) electron micrograph; bar=2 μm).

damage to the autonomic and sensory ganglion neurons leading to clinical manifestation of AASN.

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Neuropathic pain with vesical and rectal hyperreflexia and cocontraction after pelvic surgery

Pelvic and pudendal nerve injury can occur during extirpative visceral surgery such as radical hysterectomy.^{1,2} Many of these patients develop severe chronic pelvic pain

and bladder symptoms, and are often referred to neurologists with suspicion of lumbosacral plexus lesions or disc disease. There are few or no signs on examination, and patients are often considered to be "hysterical", despite having severe symptoms. Here, we describe two patients in whom severe pelvic pain and bladder dysfunction developed after hysterectomy, and who demonstrated detrusor and rectal hyperreflexia with cocontractions, features usually associated with lesions of the CNS. Whereas spinal cord sensitisation is well recognised after somatic nerve injury, our studies provide the first clear evidence for its development after visceral nerve injury in humans, and a method for its detection using ambulatory urorectodynamics.

Patient 1, a 42 year old woman, was diagnosed as having carcinoma of the cervix 5 years previously and underwent Wertheim's hysterectomy, followed by chemotherapy and pelvic irradiation. She developed severe persistent vaginal pain and hypersensitivity, which prevented her from having sexual intercourse, and subsequently bladder dysfunction, which required intermittent self-catheterisation. She received several analgesic drugs without benefit. Neurological and pelvic examination and spinal imaging, were normal. An ambulatory urorectodynamics study (after prior written informed consent) showed vesical instability associated with unstable urethral function; simultaneous abnormal rectal contractions and an associated fall in anal pressure were also recorded (figure). A repeat ambulatory study confirmed these findings, which showed clear temporal correlation with her symptoms.

Patient 2, a 69 year old woman, had had vaginal hysterectomy for prolapse with bladder repair 23 years previously. She developed severe persistent pelvic pain, exacerbated during micturition. She reported that her vagina and rectum felt continuously stretched, "as if sitting on a baby's head", and found it difficult to sit

without discomfort. She developed progressive urinary and rectal urgency. Neurological examination and anal tone were normal. Vaginal examination showed exquisite tenderness on the left. Nerve conduction study showed prolonged pudendal nerve latency (left 2.7 ms, right 2.4 ms; normal range 2.0 ± 0.2 ms).

Magnetic resonance imaging of the spine and pelvis were normal, as was flexible cystoscopy. An ambulatory urorectodynamic study (after prior written informed consent) showed urethral instability, unstable vesical contractions with simultaneous abnormal rectal contractions, and falls in anal pressure.

These patients had severe symptoms but no clinical signs, and abnormalities were detected only after pudendal nerve conduction and urorectodynamic studies, which disclosed visceral hyperreflexia in both cases. Patient 1 probably had injury to the pelvic nerves, which is well recognised after extensive hysterectomy.¹ Patient 2 had pudendal nerve damage, supported by the nerve conduction study. Our patients did not have neurological signs suggestive of CNS lesions, but demonstrated features usually associated with such lesions, namely detrusor and rectal hyperreflexia. Visceral hyperreflexia can occur after spinal cord lesions and in the absence of obvious neurogenic lesions but its occurrence after peripheral nerve damage is not well recognised.^{3,4}

The likely explanation for visceral hyperreflexia in our patients is increased barrage originating from injured sensory nerves, leading to spinal cord sensitisation; this mechanism is well established after somatic peripheral nerve injury, but rarely considered after pelvic surgery.⁵ Persistent visceral noxious input to the spinal cord could lead to reflex activation of the intermediolateral cell column,⁶ the increased output of which may in turn increase bladder and rectal contractions. Other relevant evidence of spinal cord disinhibition in our patients is the loss of the normal inhibition

Figure 1 Eight minute trace from first ambulatory study on patient 1, showing uninhibited vesical contraction, urethral instability, and abnormal rectal contraction associated with a fall in anal pressure. Note simultaneous vesical and rectal contractions (cocontractions).