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Maximum number of squats that the patient could perform in 30 seconds and the number of seconds it took to walk 10 metres at three weeks after each infusion treatment. The patient's assessment of which treatment he received is indicated as ✓ correct interpretation; × incorrect interpretation. The patient was not evaluated clinically at the end of the second placebo and IVIG cycles.

An "n of 1" trial of intravenous immunoglobulin treatment for chronic inflammatory demyelinating polyneuropathy

One small double blind study has found intravenous immunoglobulin (IVIG) to be effective in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).¹ We describe an "n of 1" trial in a patient who received IVIG and who considered that "it worked".

In 1968, when 37 years old, the man developed transient upper limb paraesthesiae. In 1970, these symptoms returned in both hands and feet together with muscle soreness and difficulty with balance. Examination showed weakness of ankle dorsiflexion, slight intention tremor of the upper limbs, areflexia, and glove and stocking sensory loss. The CSF protein was 1.9 g/l, 30% of which was γ globulin. No cells were present. Peripheral nerve conduction velocities were reduced. The next year he developed sensory loss below the knees. Treatment with prednisolone was started and the response was striking. In 1978, azathioprine was added. His subsequent course was characterised by relapses and remissions superimposed on a slow but progressive decline. In 1989, an intravenous infusion of IVIG (0.4 g/kg/day) was given for five days. Limb function improved considerably so that he no longer used a walking stick. The same dose was repeated every three weeks until November and then withheld for the next six months during which the patient's walking deteriorated. Subsequent treatment with IVIG (0.4 g/kg/month) again seemed successful, prompting a formal evaluation in September 1990.

A double blind placebo controlled single patient study was divided into four sequences of treatment, each consisting of four infusions, two placebo and two active (figure). Each infusion was given once every three weeks over 48 (4 × 4 × 3) weeks. The placebo was albumin and the study preparation was IVIG (0.4 g/kg) given over about two hours. Before the study started and immediately before each infusion, a standardised neurological assessment was made. The outcomes were (a) time to walk 10 metres, (b) maximum number of squats in 30 seconds, (c) maximum range of ankle dorsiflexion, and (d) the patient's opinion as to whether he had received IVIG or placebo. The patient declined repeated nerve conduction studies. He continued to take prednisolone (20 mg) on alternate days and azathioprine (50 mg per day).

There was no definite treatment effect objectively. The probability that the patient would correctly identify the treatment on 11 or more of the 14 occasions, however, was significant ($p = 0.03$ (one sided test)). The lack of a major treatment effect could reflect the lack of a simple, reliable, valid, and communicable measure of outcome. The time to walk 10 metres and the number of squats in 30 seconds, although objective, are insensitive and have a definite "ceiling" effect, particularly as the patient had only mild proximal weakness. Perhaps we should have timed his walking over a longer distance. The range of ankle dorsiflexion is subject to considerable within and between observer variation. Possibly the best indicator was the patient's own opinion (he was correct on all but three occasions) but it could be argued that this was not a patient blind assessment because some patients describe a "kick" soon after receiving IVIG.

Whether the lack of effect in this patient reflected the concurrent use of immunosuppressives; the severity of his "burnt out" disease with little capacity for recovery; the possibility that he may have responded to IVIG at one time, but not at another, becoming more refractory to any form of treatment as the disease advanced; the fact that he was a real "non-responder"; or we were mistaken and the patient was correct, remains unknown. Nevertheless, this study illustrates some of the difficulties that will be encountered in any randomised controlled trial, notwithstanding the considerable expense of the treatment and the time and effort it took to perform even an "n of 1" trial.

If a large trial were to be undertaken, a prespecified hypothesis should be that subgroups of patients with CIDP exist (some may respond to IVIG and others not). More importantly, better measures of outcome are necessary; patients may have different types of disability, and the accurate assessment of each demands more thought than we anticipated. Although neurophysiological studies are objective they may not reflect function and may not be tolerated. Perhaps the Rankin scale³ is the most appropriate

simple and reliable measure of functional outcome, despite being relatively insensitive. After all, if a treatment as costly as IVIG is going to be used, it should improve function by a degree that could be detected on the Rankin scale.

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Peripheral neuropathy associated with dialysis amyloidosis

Haemodialysis associated amyloidosis¹ (also called β_2 microglobulin amyloidosis²), a novel type of secondary amyloidosis, is a frequent complication in patients with chronic renal failure on prolonged maintenance haemodialysis, lasting seven or eight years. The usual manifestations are rheumatological. We describe a motor and sensory neuropathy associated with dialysis amyloidosis.

A 55 year old woman developed renal failure due to biopsy proved crescentic glomerulonephritis and had been on maintenance haemodialysis with cuprophane membranes for 10 years. After eight years on dialysis she developed weakness and numbness and dysaesthesia in the lower extremities. In August 1992, she was admitted to our hospital for evaluation of these symptoms. Her medical history and family history were unremarkable. Cranial nerves and autonomic function were normal. There was distal weakness and wasting of the lower but not of the upper limbs. Sensory examination showed distal and symmetric hypoaesthesia in the lower limbs, involving all modalities of sensation. Tendon reflexes were normal at the knees and absent at the ankles. There were no pathological reflexes, no signs of carpal tunnel syndrome, and no signs of systemic amyloidosis.

Routine blood tests were normal. Serum β_2 microglobulin concentration was 86.4 mg/l (Pharmacia radioimmunoassay; normal <3 mg/l). There was no Bence-Jones proteinuria or a monoclonal immunoglobulin on serum protein electrophoresis. Moderate amounts of long duration polyphasic high amplitude motor units were found by EMG in the muscles of the lower limbs. The motor nerve conduction velocity

and the sensory nerve conduction velocity were 50.5 and 63.4 m/s for the right median nerve. There were no electrical responses from the right posterior tibial nerve or the right sural nerve.

Biopsy of the left sural nerve showed considerable reduction in the number of myelinated fibres. Electron microscopy showed a loss of unmyelinated fibres. Teased fibre studies and electron microscopy confirmed a primary disorder of the axons. There were amyloid deposits in the endoneurium and perineurium, and around vessels in the epineurium, which stained positively with Congo red and showed characteristic apple green birefringence under polarised light. Under the electron microscope, each fibril was 6–12 nm in diameter and 100–600 nm in length. Fibrils were parallel and tightly packed, forming a short bundle. These findings were in agreement with the characteristic structure of the amyloid fibrils in dialysis amyloidosis.³ This amyloid substance was shown to be β_2 microglobulin by immunohistochemical staining (figure (A)). Amyloid A protein, prealbumin, and κ or λ chains of immunoglobulin were absent immunohistochemically (figure (B)). Our findings differed from other reports of primary and secondary amyloidosis, in which the amyloid fibrils were distributed in different directions without forming bundles.

Peripheral neuropathy is an established complication of chronic renal failure. Although the metabolic derangement responsible for uraemic neuropathy is unknown, it is probably secondary to the accumulation of uraemic toxins. Because chronic haemodialysis stabilises peripheral nerve function in most patients with chronic renal failure, the occurrence of clinically evident neuropathy in patients on chronic haemodialysis has become uncommon. Muscle cramps and the restless legs syndrome, common symptoms of uraemic neuropathy,⁴ were not present in our patient. Thus chronic renal failure was an unlikely cause of the neuropathy.

The mechanism of peripheral neuropathy in amyloidosis is not known, although several hypotheses have been suggested. In our case, the serum β_2 microglobulin concentration was very high, and the deposition of β_2 microglobulin as the amyloid substance was present in the sural nerve. If the patient had had primary amyloidosis, she would not have survived for 10 years and there would have been other signs of primary amyloidosis. The biopsy findings are compatible with those of amyloid neuropathy, either primary or familial, showing a predominance of axonal degeneration.⁵

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Immunohistochemical staining with antiserum to β_2 microglobulin (A) and antiserum to amyloid A protein (B) of the sural nerve. The amyloid substance is positively stained with antiserum to β_2 microglobulin (bar = 50 μ m).

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Subacute cerebellar degeneration and Lambert-Eaton myasthenic syndrome associated with antibodies to voltage-gated calcium channels: differential effect of immunosuppressive therapy on central and peripheral defects

Several reports have described a neurological disorder in patients with cancer, manifesting as subacute cerebellar degeneration (SCD) and Lambert-Eaton myasthenic syndrome (LEMS).^{1–3} Autoantibodies, possibly directed against voltage-gated calcium channels (VGCCs), may play a part in the pathogenesis of this syndrome.^{4–6} We report a patient with non-Hodgkin's lymphoma who developed SCD and a LEMS-like neuromuscular disorder. Onset of these symptoms was associated with very high

amounts of anti-VGCC antibodies in the patient's serum and CSF. We describe here the differential response of neuromuscular, but not cerebellar, symptoms to immunosuppressive treatment and the associated changes in titres of anti-VGCC antibodies in the serum. This patient (patient 6) was included in a previous report.²

A 55 year old woman was well until July 1989 when she noted right supraclavicular adenopathy. A biopsy showed non-Hodgkin's lymphoma. A staging procedure for metastatic disease was negative. The patient underwent radiation therapy to the neck one month later. She was then well for the next three months when she noted the onset of slurred speech. In January 1990, she developed worsening dysarthria as well as diplopia, ptosis, vertigo, nystagmus, and a clumsy gait. An edrophonium test was negative and multiple brain MRI scans were normal. Lumbar puncture showed clear CSF under normal pressure. There were 9 mononuclear cells/mm³, normal CSF protein, and negative cytology. Oligoclonal bands were noted with a normal CSF IgG index. Serum antiacetylcholine receptor antibody and antiPurkinje cell antibody (Yo) were negative. A clinical diagnosis of SCD was made.

In June 1990 there was onset of proximal muscle weakness affecting the upper and lower extremities without sensory change or sphincter dysfunction. There was no evidence of autonomic dysfunction. Mental state was normal. Ptosis, disconjugate gaze, and nystagmus were seen bilaterally. Other cranial nerves were normal. Motor examination showed normal bulk and tone without fasciculations. Strength was 4/5 in proximal upper and lower extremity muscles. Distal muscles were 5/5. No improvement of strength was noted with exercise. Sensory examination showed mildly decreased vibration sensitivity in the lower extremities with normal pain, temperature, and position sensation. There was moderate dysmetria in the upper and lower extremities. Gait was wide based with poor tandem walking. Romberg's sign was absent. Deep tendon reflexes were normal in the upper extremities and mildly reduced in the lower extremities. The plantar responses were flexor bilaterally.

Repeat oncological evaluation was unrevealing. Brain MRI was normal without cerebellar atrophy. Serum protein electrophoresis and tests for HIV, creatine phosphokinase, B12, folate, venereal disease, antiacetylcholine receptor antibody and anti-DNA antibodies were negative or normal. Tests for serum anti-Yo, Hu, and Ri antibodies were negative. Oral prednisone was started at 100 mg every other day in September 1990 and azathioprine (150 mg per day) was added in May 1991.

Electrophysiological evaluation in August 1990 showed normal motor and sensory nerve conduction velocities and distal latencies. Repetitive stimulation of the ulnar nerve at 2 Hz recording from the abductor digiti minimus showed a 28% decrement with post-tetanic potentiation of 90%. Stimulating the peroneal nerve and recording from the extensor digitorum brevis there was a 28% decrement and post-tetanic potentiation of 600%. Compound muscle action potential amplitude (baseline to negative peak) obtained with supramaximal stimulation was 3 mV in the abductor digiti