LETTERS TO THE EDITOR

Chronic inflammatory demyelinating polyneuropathy during treatment with interferon- α

Interferon- α (IFN- α) is widely used for the treatment of chronic viral hepatitis. There have been some reports concerning the development of autoimmune diseases, particularly thyroid disease, in patients under treatment with IFN.¹ Disorders including autoimmune haemolytic anaemia, pernicious anaemia, thrombocytopenic purpura, systemic lupus erythematosus, Raynaud's disease, parotiditis, and epididymitis have been reported. Some neurological problems have also been described²; although most such adverse events have involved the CNS, several cases of peripheral nervous system involvement have been reported—namely, axonal polyneuropathy,³ neuralgic amyotrophy, multiple mononeuropathies, and myasthenia gravis.⁴ On the other hand, some authors have reported that IFN- α may be an effective alternative therapy in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) who are refractory to conventional treatments.⁵ Two trials using IFN- α and IFN- β on patients with CIDP are currently in progress. We describe one patient who developed CIDP during IFN- α treatment.

A 29 year old man who had hepatitis C for 2 years, was started on IFN- α treatment. He had the usual related flu-like syndrome during the first month of treatment. Previously he had had some migraine headache episodes, but no other medical problems. After 4 months of treatment, he progressively developed paraesthesia and weakness in both feet. When he came to our hospital 4 months later, his condition had worsened. Neurological examination disclosed tetraparesis (proximal and distal) with 4/5 strength (Medical Research Council scale), generalised areflexia, and hypoaesthesia both in his hands and feet. EMG data are summarised in the table. Prolonged distal motor latencies, slowed conduction velocities, temporal dispersion of the compound muscle action potentials (CMAPs), marked prolongation of F wave latencies, and a reduction of sensory and motor CMAPs in both arms and the right sural nerve were found. These findings were consistent with a demyelinating polyradiculoneuropathy with a mild axonal

degeneration. The protein concentration in CSF was 208 mg/dl, there were no cells. Immunoelectrophoresis was normal, and antiganglioside antibodies (GM1, GD1a, GD1b, GT1b) were absent. Serum biochemical studies, including HIV antibody determination, were negative. We ruled out the presence of cryoglobulins. Although IFN- α was discontinued, the disease continued to worsen; the maximal neurological deficit was reached 5 months from onset. The patient was given prednisone (60 mg/day) and progressively improved. One year later he had no symptoms and showed areflexia only on neurological examination. A further EMG showed appreciable improvement.

This is the first report of CIDP development during treatment with IFN- α . CIDP is an immune mediated disorder that usually responds to plasma exchange, intravenous gammaglobulin, or corticosteroids, although occasionally the disease is refractory to these therapies. In the past, some authors have reported improvement in patients with CIDP who were receiving IFN- α .⁵ The mechanism by which IFN induced improvement in these patients is uncertain, although it may be related to complex immunomodulating effects, possibly by reduction of proinflammatory cytokine concentrations (tumour necrosis factor and IFN- γ) which may have a role in the development of inflammatory demyelination.⁵ The relation between IFN- α and CIDP in our patient is uncertain. Whether IFN- α was the cause of CIDP or whether their relation was only coincidental remains unknown. Nevertheless it seems clear that the treatment mentioned above did not prevent the development of this demyelinating disease with an immunological basis. IFN- α exerts complex immunomodulator effects, it can improve or worsen autoimmune diseases.

Although our findings could be coincidental, the data suggest caution, as IFN- α treatment might yield undesirable effects involving autoimmune phenomena.

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Posteroventral pallidotomy can ameliorate attacks of paroxysmal dystonia induced by exercise

Paroxysmal exercise induced dystonia is a rare disorder classified as one of the paroxysmal dyskinesias.^{1,2} In this condition patients develop dystonia, mostly involving their feet, after prolonged exercise, usually walking or swimming.^{1,3} Treatment response is poor to both antiepileptic drugs and drugs given for dystonia—for example, anticholinergic drugs, muscle relaxants, or acetazolamide.³

We recently noted the dramatic benefit of unilateral pallidotomy in completely abolishing attacks of paroxysmal exercise induced dystonia of the contralateral foot in one patient.

This 47 year old woman was followed up over 2 years for a 10 year history of attacks of dystonia affecting her right foot, induced by exercise. At onset the attacks were mild and were induced by walking long distances. During an attack her right foot would invert for a few minutes making it difficult for her to continue walking or stand. The attack would subside within 2-3 minutes on resting. Two years after onset the attacks subsided and she was attack free for 3-4 years. Four years ago the attacks returned and got progressively worse, increasing in frequency and intensity. Over the past 2 years she could have an attack on walking even 10-15 steps. The attacks in the past few years not only made her right foot to turn as before but caused her to fall as the right leg would rise up in the air and flex at the knee and hip and there would be some involvement of the trunk causing her spine to twist to the left. Recently the toes of the left foot were also noted to curl up during attacks. She would never lose consciousness and the attacks would last 1-2 minutes and then subside. They never occurred in sleep. Interictally the neurological examination was normal although posturing of the right foot could be induced by repeated prolonged passive flexion-extension movements of the right ankle. More recently she also began to have occasional spontaneous attacks. Investigations including repeated MRI of the head and spine were normal as were tests for Wilson's disease and other causes of secondary dystonia. Examination of CSF gave normal results and disclosed no oligoclonal bands. The patient was negative for the common mitochondrial mutations. An EMG/nerve conduction study detected no evidence of a peripheral neuropathy and somatosensory evoked potentials were normal. Polymyography confirmed cocontraction of agonists and antagonist muscle pairs in the right leg during an attack supporting an organic basis for the dystonia. Surface EEG during an attack and interictally disclosed no abnormality. The patient was tried on a variety of treatments including baclofen, levodopa, benzhexol, tetrabenazine, and acetazolamide without benefit. Different antiepileptic drugs given individually or in combination (1g sodium

Nerve conduction studies

	Distal latency (ms)	Conduction velocity (m/s)	Amplitude (μ V (sensory) mV (motor))
Sensory:			
Right median	3.1	50	4.2
Right ulnar	2.7	48	1.1
Left sural	2.8	41	8.5
Right sural	3	43	3.3
Motor:			
Right median	4.4	34	2.4
Left posterior tibial	10	39	0.8
Right common peroneal	7.9	38	3.6
F wave:			
	Latency F-M	Incidence (n (%))	
Right median	42.9	30 (100)	
Right ulnar	36.3	31 (60)	
Left posterior tibial	65.5	57 (70)	
Right common peroneal	63.7	57 (70)	

valproate with 1 g carbamazepine, and 2 m clonazepam a day) also did not help. The failure of the medical treatment and the frequency of up to 10 or more attacks a day made normal functioning impossible for the patient and therefore a surgical option was considered particularly as the attacks were mainly unilateral. With the consent of the patient a left posteroventral medial pallidotomy was carried out as in a previously described technique.⁴ She made an uneventful recovery and had no neurological complications. Immediately after operation the attacks of exercise induced dystonia had ceased completely having occurred more than 10 times a day immediately before the operation even on walking 10–15 steps. At the end of 6 months follow up she had been attack free, apart from occasional minor spasms of her left foot on exercise, despite normal activities; anticonvulsant treatment was gradually being withdrawn.

This is the first example of the usefulness of pallidotomy in a patient with any form of paroxysmal dyskinesia. Pallidotomy and more recently pallidal stimulation are currently being used as surgical techniques for advanced Parkinson's disease in patients with complications of levodopa treatment.⁵ These procedures are particularly helpful in abolishing the levodopa induced dyskinesias.³ Pallidotomy has also been found beneficial in patients with generalised dystonia⁶ and recently a unilateral pallidotomy was reported to produce bilateral benefit in one patient with tardive dyskinesia.⁷

Given the improvement in our patient a unilateral pallidotomy could be considered as a treatment option in patients with stereotyped paroxysmal attacks as occur in paroxysmal exercise induced dystonia and the other paroxysmal dyskinesias such as paroxysmal non-kinesigenic dyskinesias in which treatment is often unsatisfactory.² A bilateral procedure could be considered in patients with bilateral attacks such as patients with paroxysmal non-kinesigenic dyskinesias who are unresponsive to drug treatment as bilateral pallidotomy seems to improve patients with generalised dystonia.⁶

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Sudden appearance of invalidating dyskinesia-dystonia and off fluctuations after the introduction of levodopa in two dopaminomimetic drug naive patients with stage IV Parkinson's disease

Hyperkinesias (dystonia, dyskinesia) are, with fluctuating akinesias, the most debilitating disturbances appearing during the advanced course of Parkinson's disease.¹ The origin of these disturbances is controversial; as hyperkinesias are seen after long term treatment with levodopa or dopaminoagonist drugs many researchers think that these motor fluctuations could be prevented by dopaminomimetic drug restriction,¹ others think that hyperkinesias will appear anyway after enough years, independently of dopaminomimetic drug restriction—that is, the supersensitivity of striatal structures to external administration of dopaminomimetic drugs is an epiphenomenon of natural degeneration in Parkinson's disease.²

Ten years apart from one another we had the chance to observe two patients with Parkinson's disease with prevalent akinetic symptoms who came to us already in an advanced stage of Parkinson's disease, classified as stage IV according to the Hoehn and Yahr scale.³ These patients had never been treated with dopaminomimetic agents (levodopa, dopaminoagonists), or amantadine or anticholinergic drugs, and both developed dyskinesias and motor fluctuations when levodopa was increased to the amounts commonly used in patients with stage III–IV Parkinson's disease treated for 6–10 years.

Patient 1 was a 76 year old man living in the inner mountainous part of central Italy. When he came to us he was incapable of rising from his bed; hypomimia, akinesia, flexed dystonic posture, and rigidity were rated 20 at motor examination with the unified Parkinson's disease rating scale (UPDRS),⁴ modest 4–5 tremor was present at the upper limbs, left and right intensity was rated 4 at the UPDRS, and utterances were feeble and incomprehensible. The total UPDRS score was 126 (SD 4).

It was possible to reconstruct his clinical history from relatives, and apparently his early stooped posture and akinetic disturbances had appeared at least 10 years before, but was considered to be due to severe arthrosis and was treated with salicylates. Brain MRI at admission was normal. Early treatment with 62.5 mg levodopa thrice daily+benserazide did not induce gastrointestinal intolerance but did not change his UPDRS score and was rapidly (4 days) increased to 250 mg levodopa four times daily+benserazide. Oromandibular dyskinesias, dystonic neck and trunk leftward rotations, and left leg dyskinesias were noticed 2 days after the 1g daily levodopa dosage was reached. Dystonic-dyskinetic movements appeared 20–30 minutes after the first (7 00 am) 250 mg levodopa+benserazide tablet, lasted through the day, and were painful, mostly in the afternoon.

His UPDRS scores were 72 (SD 3) from 8 00 am to 2 00 pm, 88 (SD 3) from 2 00 pm to 8 00 pm. Dyskinesia-dystonia scores were 11 (SD 2) from 8 00 am to 10 00 pm and 13 (SD 2) from 2 00 pm to 10 00 pm. Because dyskinetic-dystonic movements were not tolerated, the daily levodopa had to be reduced to 62.5 mg every 3 hours (total 375 mg/day). With this treatment UPDRS scores were 86 (SD 4); oromandibular dyskinesias and

torsional dystonias were still present and rated 10 (SD 2). Bromocriptine up to 10 mg/day was not tolerated. During the next 2 years levodopa treatment could not be increased. His UPDRS scores were 89 at 2 weeks before his sudden death due to apparent cardiovascular complications with cardiac arrest. A postmortem examination showed anteroinferior myocardial infarction, and normal brain structures with depigmentation of the nigral structure. Mesencephalic structures were cut into horizontal 7 µm thick sections and stained with haematoxylin and eosin; three Lewy bodies were found in 109 identified pigmented cells and cell loss was about 86% compared with age matched controls and literature reports.⁵

Patient 2 was a 72 year old man from the same region of central Italy. He came to us akinetic and rigid, with a stooped posture and minor tremor of both upper limbs, and was confined to a wheelchair. Utterances were feeble and incomprehensible. His total UPDRS motor score was 93 for upper limbs, rest tremor was only 2. He had been incapable of walking during the past year, and spent his time on a chair, where he also slept. His relatives described the progressive deterioration in the past 10 years, from the stooped posture to progressive akinesia and language and walking deterioration. His disturbances were attributed to senescence-arthritis, until comparison with other patients with Parkinson's disease living in the same region, prompted the neurological consultation. This patient was treated with increasing doses of levodopa+benserazide after a one week trial with 125 mg thrice daily had not changed his UPDRS score. A 1.5 g daily dose of levodopa (in 6 administrations) was reached in the next week. Oromandibular dyskinesias and leftward torsion dystonias appeared in the same week. He became able to walk unaided but tremor of the upper limbs was still present, at rest and during walking. His dyskinesias were uncomfortable, although not painful, and his stooped posture was only slightly modified (score 3 from 4). His UPDRS score during treatment was 57, tremor score was 4, and dyskinesia-dystonia score was 7 (SD 1). Treatment was then reduced to 500 mg levodopa+benserazide with 15 mg ropinirole (increasing in three weeks from 1.5 mg/day). With this treatment dyskinesias were reduced, UPDRS score for dyskinesias was 4 in the morning, 5 in the afternoon, and he was able to walk unaided in the morning. His UPDRS score was 65 (SD 4) in the morning and 79 (SD 2) in the afternoon. Brain MRI was normal.

In conclusion, both patients came to us with a levodopa responsive parkinsonism that had appeared, according to history reconstruction, at least 10 years before. Both could be considered at least in stage IV of the Hoehn and Yahr scale.³ Both had never been treated with dopaminomimetic drugs or with other drugs currently used in the treatment of Parkinson's disease. In both patients dyskinesias and dystonias, accompanied by motor fluctuations throughout the day, appeared in the first week. After that a levodopa dose able to modify the akinesia and rigidity scores was reached. Reduction of levodopa dosage in patient 2 and introduction of a dopaminoagonist improved dyskinesia but the total UPDRS score was higher than the score obtained with 1.5 g/day levodopa.

These findings favour the hypothesis suggesting that hyperkinetic fluctuations are not dependent on prolonged dopaminomimetic drug administration but on the natural