Myasthenia gravis in a patient with chronic active hepatitis C during interferon-α treatment

Batočci et al. recently reported the occurrence of autoimmune myasthenia gravis during interferon-α (INF-α) treatment in two patients with malignancies. We report a patient who developed myasthenia gravis after INF-α treatment for chronic hepatitis C. A previously healthy 54-year-old man developed malaise and dyspepsia three years ago. Increased serum concentrations of alanine aminotransferase and aspartate aminotransferase led to a serological diagnosis of hepatitis C infection. Liver biopsy showed a histological picture of chronic active hepatitis. Two years later, in March 1993, the patient received INF-α 1 (Wellferon, Wellcome, UK) subcutaneously at a dose of 9 x 106 U on alternate days. After nine months of treatment, in November 1993, he began to complain of intermittent diplopia. Ophthalmological evaluation disclosed slight left rectus muscle paresis. Both CT and MRI of the brain were normal. No treatment was given. The one-year INF-α cycle was completed (February 1994). Diplopia lasted until September 1994, when the patient came under our observation. Neurological examination showed slight left rectus muscle paresis with diplopia on the left gaze, slight right eyelid ptosis which appeared after two minutes of forced upward gaze, and neck flexor muscle fatigability. Single fibre electromyography showed an increased jitter from frontal muscles (mean consecutive difference (MCD) = 72 s, normal age matched MCD range 40-63 s). We recorded saccadic eye movements from his clinically unaffected right eye (to prevent double vision we occluded his left eye). His hypometric saccades (mean accuracy value 83%) turned to ophthalmoparesis after parental neostigmine. Routine laboratory analyses were normal except for a polyclonal increase in serum gammaglobulins and in creatine kinase (299 IU, normal <190 IU). Thyroid function tests, and antibodies to nucleic, smooth muscle, mitochondrial, and serum lactate were normal. Serum anti-acetylcholine receptor (anti-AChR) antibody titre was 73.6 nmol/l (normal <1 nmol/l). MRI of the mediatinum was normal. Oral pyridostigmine treatment induced pharmacological remission except for slight left ptosis, which persisted at the last visit (July 1995) even after stopping pyridostigmine. Serum creatine kinase, alanine aminotransferase, and aspartate aminotransferase were normal. Anti-AChR antibodies were present at a concentration of 18.5 nmol/l.

This is the third reported case of autoimmune myasthenia gravis occurring after INF-α treatment, the first in a patient treated for chronic active hepatitis. In our patient, myasthenia gravis was virtually confined to ocular muscles. Riedel et al. described a patient with AIDS with a transient ocular pseudomyasthenic reaction that was strictly dependent on a single injection of INF-α. The two patients with malignancies treated with INF-α reported by Batočci et al. fulfilled the diagnostic criteria for myasthenia gravis, had generalised myasthenic symptoms, and responded to pyridostigmine, and showed persistent, low concentrations of serum anti-AChR antibodies. One of them also had laboratory and muscle biopsy findings that suggested mitochondrial myopathy. Our patient developed symptoms of myasthenia gravis after nine months of INF-α treatment for chronic active hepatitis. The diagnosis of myasthenia gravis was made seven months after INF-α discontinuation. Anti-AChR antibody titre was high, but fell to an intermediate titre after 10 months. Autoimmune mechanisms seem to be involved in the pathogenesis of both myasthenia gravis and chronic active hepatitis. INF-α is an immunomodulating cytokine that down regulates MHC class II expression on lymphoid cells and reduces active inflammation. These properties have led to its use as a treatment for chronic actinic chronic active hepatitis. In this disease, INF-α could also induce down regulation of a class I MHC restricted immune response.4 A rationale for INF-α treatment in myasthenia gravis has been recently suggested by Shenoy et al., on the basis of its therapeutic efficacy on experimental autoimmune myasthenia gravis.4 Although our finding could be coincidental, all these data suggest caution, as INF-α treatment might yield undesirable effects involving autoimmune phenomena—for example, by CD8+ T cell mediated perturbation on the "regulatory circuit" with lack of homostatic response.5

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Development of myasthenia gravis during interferon-α treatment for anti-HCV positive chronic hepatitis

We report a case of severe myasthenia gravis during interferon-α 2a therapy for anti-HCV positive chronic hepatitis in a patient with evidence of genetic predisposition to myasthenia gravis.

A 64-year-old white man underwent a blood transfusion after prostatectomy for cancer (T2, N0, M0, G1). Five years later, he was given human recombinant interferon-α 2a at a dose of 5 million units (MU) three times a week, for post-transfusional anti-HCV positive chronic hepatitis. After six weeks of treatment, he began complaining of fluctuating weakness of his neck, eyes, and throt muscles, difficulty in raising his head, right palsy, and fading voice after sustained conversation.

A brother three years older had had myasthenia gravis which was successfully treated with thymectomy for thymic hyperplasia.

Neurological examination showed weakness of muscles of the neck and shoulder girdle, increasing after physical effort. Right ptosis, dysphonia, and difficulty in mastication, swallowing, and breathing. Pronounced improvement occurred 10 to 15 minutes after 1 mg neostigmine injected intramuscularly. No decrement of the compound muscle action potential on repetitive nerve stimulation was seen. Anti-AChR antibodies were present in blood with a titre of 12 pmol/ml (normal, 0 pmol/ml).

Six months after starting interferon treatment, he was discharged for red cell, white cell, and platelet count, serum protein electrophoresis, transaminases (before the beginning of interferon treatment, ALT was 124 units/l, and AST was 148 units/l), lactate dehydrogenase, muscle enzymes, and thyroid hormones. Erythrocyte sedimentation rate was 23 mm/h and potassium 3.2 mEq/l. Specific prostatic antigen was also normal (<1 ng/ml). Typing for HLA major histocompatibility complex (MHC) showed HLA A2-A3 antigens. Medialateral CT and radionuclide bone scan were normal.

The patient stopped taking interferon and was seven years post-transfusional treatment. Eight days later, he went into a sudden severe respiratory crisis and was admitted to the intensive care unit, where he received plasmapheresis and corticosteroid treatment. His clinical condition quickly improved: his respiration returned to normal, he was able to sustain his head, and to raise his arms beyond his shoulders repeatedly; his voice became clear again and he did not show the same fluctuating problems as in the past. He was discharged on anticholinesterase and corticosteroids and eight months later he was asymptomatic on very low doses of methylprednisolone.

In this case, Batočci et al. reported two patients who developed typical myasthenia gravis during interferon-α 2b treatment. Both patients had raised anti-AChR antibody titre but neither of them had evidence of genetic predisposition to myasthenia gravis. The ocular symptoms, such as ptosis of the left eyelid and intermittent diplopia, of the patient described by Riedel et al. occurred two hours after interferon-α injection, persisted for the period of treatment, and subsided after treatment was stopped. They were not associated with any of the diagnostic criteria for myasthenia gravis, suggesting a pseudo immigrant reaction rather than a dose or million use myasthenia induced by interferon treatment.

Our patient developed acute myasthenia after six weeks of interferon-α treatment at a dose commonly used for anti-HCV positive chronic hepatitis. There may be a genetic predisposition to myasthenia gravis as he had a brother affected by the same disease and he did not show the same fluctuating problems as in the past, but interferon-α treatment should not be given or at least given very carefully, to patients with evidence of familial myasthenia gravis.

Interferon-α treatment should not be given or at least given very carefully, to patients with evidence of familial myasthenia gravis.
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2 Riedel RR, Schmitt D, Herrman HL-A. Manometric features of mitocondrial DNA 8993 T > G point mutation in several members of a family, two of which had infantile spasms as the presenting symptom and mental retardation thereafter. We found an uncommon disease as a cause of infantile spasms. Further, we are not aware of any previous report on the association of infantile spasms and a developmental delay. This does not necessarily mean that this association is exceptional as the biochemical origin they have been undiagnosed.


Respiratory chain complex I deficiency in an infant with infantile spasms

Infantile spasms are a common epileptic disorder of infancy that can be caused by a great variety of brain diseases of metabolic, developmental, chromosomal, perinatal anoxic, and postnatal origin. The number of metabolic disorders associated with infantile spasms is restricted to peroxisomopathies, syndromes, phenylketonuria, non-ketotic hyperglycaemia, and pyridoxine deficiency. We report an infant with a complex I deficiency of the respiratory chain whose presenting and most conspicuous symptom was infantile spasms. On reviewing the literature, we were aware of two conditions, rare diseases.2,3

A 7-month-old boy infant whose prenatal, neonatal, and postnatal history was irrelevant, began to have episodes of spasms several times daily. Developmental milestones were within the normal range. Examination showed mild hyporeflexia. But was otherwise normal. Frequent typical flexor spasms on awakening and in the first stage of sleep were seen. An EEG showed diffuse consistent abnormalities compatible with cerebral atrophy. The patient was treated with ACTH for six weeks. Both the spasms and the hypsarrhythmia disappeared after the first week of treatment and did not recur. Brain CT was normal. Several blood lactate determinations disclosed a consistent hyperlactataemia (60–80 mg/dl) together with normal blood pyruvate. The 24 hour urinary excretion of succinate, fumarate, glutarate, 2,3-dihydropseudohydrate, and lactate were increased. Acetylcarnitine, depyruvated carnitine, and Krebs' cycle enzymes in fibroblasts were within normal limits. The activities of the respiratory chain complexes in muscle mitochondria (corrected for the activity of citrate synthase) were within the normal range, except for NADH-cytochrome C reductase, which was very reduced. This finding was compatible with complex I deficiency. The infant was given oral coenzyme Q, carnitine, riboflavin, and succinate for the next three years. Lactate concentrations have remained mildly increased (40–50 mg/dl), but he has not had further seizures. At four years of age he showed a mild muscle wasting of proximal distribution, and developmental dysphasia. A muscle biopsy at this age disclosed no definite pathological abnormalities; respiratory chain metabolism in muscle yielded similar results to the previous study. Seizures, typically partial or myoclonic, are a recognised feature in patients with certain mitochondrial disorders.4 However, we are only aware of two previous reports of the association of infantile spasms with a presumed mitochondrial disease. Kamoshita et al were the first to describe the appearance of infantile spasms in a patient with putatively established subacute necrotizing encephalomyelitis.5 This disease may be associated with errors of metabolism affecting the respiratory chain or other pathways, but the authors did not provide any biochemical study to suggest a specific metabolic disorder. On the other hand Mäkelä-Benga and al have recently described a mitochondrial DNA 8993 T > G point mutation in several members of a family, two of which had infantile spasms as the presenting symptom and mental retardation thereafter.6 We found an uncommon disease as a cause of infantile spasms. Further, we are not aware of any previous report on the association of infantile spasms and a developmental delay. This does not necessarily mean that this association is exceptional as the biochemical origin they have been undiagnosed.

The case reported also shows a rare phenotype for complex I deficiency, but the clinical range of mitochondrial diseases is expanding.7 Despite the few cases reported infantile spasms should be considered as one of the forms of presenta- tion of mitochondrial diseases. It also seems advisable to suspect a respiratory chain disorder in infants with the so-called crypto- genetic West syndrome.

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Semantic neglect

An aphasic woman with a left posterior hemisphere stroke showed a decreased ability to cancel right sided stimuli when the cancellation was based on matching a picture with a verbal name and description. She showed normal performance on traditional cancellation tasks.4 The neglect was manifested when the object was shown to her visually. This 49 year old right handed woman was admitted for "decreased speech." For one day she had spoken only in short, automatic phrases. Commands were obeyed inconsistently, she did not repeat, and her comprehen- sion was preserved. Coulter and de Wernicke described the Western aphasia battery7 given 12 days after her ictus, showed an aphasia quotient of 22:8, with the pattern of Wernicke’s aphasia. The remainder of the general neurological examination was normal.

A remote right posterior parietal infarction and an acute left posterior temporal-parietal infarction seen on MRI was thought to be secondary to an autoimmune hypercoagulable state. No evidence of a positive anamnestic history was negative and the patient had a pre-stroke history of an autoimmune haemolytic anaemia, myasthenia gravis, and lupus anticoagulant.

The patient only identified named pictures on her left but was able to cancel objects well on the right and left sides in a routine cancellation task. To test the impression that the patient was neglecting semantic material on her right a series of cancellation tasks were given.

At the first examination (one week after the stroke) the patient was given two variati- ons of cancellation task: a routine version and a semantic version.4 The routine version was similar to the standard method developed for assessing neglect in aphasic patients.2 For the semantic version the patient was asked to cross out specific objects by name and description (for example—Where is the pen- cil? The item that you would use to write on a piece of paper?).

On the routine cancellation task the patient cancelled a total of 42 of 45 right sided targets and 42 of 45 left sided targets. There was no difference when the paper was placed to the left or right. Pooling all the semantic task trials 56 of 80 left sided items and 56 of 80 right sided items were cancelled (P = 0.004, Yates’s correction χ² = 8–32, df = 1). Placing the entire page to the patient’s left or right did not change performance. Of the 30 semantic items used 12 were detected more often when they were on the left, three when they were on the right, and 15 were detected equally regardless of side (P = 0-02, χ² = 7-8, df = 2).

Was the patient’s performance due to differential attentional demands for the two versions of the test? In the traditional cancellation task the patient was simply finding any object on the page. In the second version of the task she had to find a specific individual object. To evaluate if this mechanism explained the patient’s performance, the patient was restested 12 weeks after the stroke. The mechanics of testing were simi- lar to the first examination.

In the routine task the patient was asked to cancel all the objects on a page regardless of identity or location. In the pictorial version she was shown a picture of the object she had to cancel. In the differential version of the task the patient was told object to which patient’s performance improved in the three months since her ictus.

She was successful on the routine and the semantic task. She showed a disproportionate number of errors in the identification of objects on the right side of the page when they were named verbally when they were presented visually or when they were cancelled regardless of their identity (χ² = 14-9, df = 5, P = 0-01). When the patient was asked to cancel objects named verbally and described visually there was a significantly greater risk of omission if the object to be cancelled was located to the patient’s right. Her performance was not due to an inability to see or attend to the