Improvement of Isaacs' syndrome after treatment with azathioprine

In Isaacs' syndrome, muscular cramps exacerbated by effort, stiffness, delay in muscle deconaction, myokymia, fasciculations, and excessive perspiration are associated with repetitive electromyographic discharges. The peripheral origin of the neuromyotonic discharges has been accepted since Isaacs' first description, but the exact aetiology remains obscure.

Sinha et al reported experimental arguments for an autoimmune process leading to qualitative reduction of the potassium channels on the axonal membrane. Three patients had antibodies from sera exchange; and three from azathioprine. We report another favourable response to azathioprine.

A 36 year old patient was admitted in February 1991 with a five month history of progressive paraesthesia of all four limbs, diffuse painful cramps affecting distal muscles, and stiffness. He was regularly treated with insulin for diabetes diagnosed in 1983.

Examination showed delayed muscular relaxation of the masseter and limb muscles exaggerated by repetitive movements, without loss of strength or muscle hypertrophy. There were repetitive tendon reflexes and palmar and plantar dysaesthesiae. Myokymia was seen in the interosseous muscles of the hands. There was no sensory loss. Hyperhidrosis was noticed. The patient experienced episodes of transient diplopia. Ophthalmological examination disclosed a slight reduction of abduction of the left eye and horizontal nystagmus. Two days later, there was an impaired right eye elevation, but no longer any involvement of the left eye.

The following laboratory investigations were normal: serum electrolytes including calcium and magnesium, enzymes, blood count, serum immunoglobulin concentrations, thyroid function tests, cortisol concentration AbAlC, tumour markers. Serum tests for HIV, CMV, EBV, hepatitis A, B, and C, Borelia burgdorferi, echo, cossackie, influenza, and parainfluenza were negative. IgG antibodies to HHV1, VZV, and measles were weakly positive. Tests for autoantibodies were negative including antinuclear, anti-DNA, antinucleolar muscle, antismooth muscle, antimitochondria, antiarthritis, and antipancreatic islets. Analysis of CSF was normal, including cell count and immunoglobulin concentration.

Sural nerve biopsy showed endoneurial oedema, a mild loss of myelinated fibres, narrowed myelin sheaths, and in some places, vacuolisation and partial unrolling of the myelin sheaths.

On 15 February an EMG examination, disclosed neuromyotonia predominantly in the distal muscles of the hands and the right extensorum digitorum brevis, with spontaneous activity arising at rest, in a pattern of brief bursts of repetitive motor unit discharges with high interspike frequency. Stimulation of the nerves elicited these bursts, appearing after the M waves. Fibrillation and denervation activities were seen, particularly in the right extensorum digitorum brevis. Motor and sensory conduction velocities were normal; F responses were present with normal latencies but sometimes the compound discharges preceded their appearance.

Diagnosis of Isaacs' syndrome was made and treatment was begun with carbamazepine. A remarkable decrease in frequency and amplitude of neuromyotonic bursts was observed. Despite the beneficial effect of carbamazepine (600 mg/day), this drug had to be discontinued after a few days because of cutaneous allergic reaction.

Phenytoin induced a similar allergic effect and was also discontinued. Azathioprine was begun in May 1991 (2.5 mg/kg). In September, painful stiffness of the hands and especially of the legs had clearly diminished. The chronic myokymia and finger pulp hypaesthesia persisted, as well as some degree of neuromyotonia. An EMG in December 1991 showed improvement with persistence of neuromyotonic bursts only in the arms. An EMG in December 1992 showed almost complete disappearance of neuromyotonia. In April 1993, nearly two years after initiation of azathioprine treatment, there was a dramatic reduction of pains in the legs and disappearance in the feet. Epidodic diplopia had disappeared.

Since the initial two cases described by Isaacs, some 40 cases have been reported under various terms including neuromyotonia pseudomyotonia, au gustinian myotonia, and continuous muscle fibre activity. This syndrome has been described in association with polyradiculoneuropathy, pulmonary small cell cencer, or thymoma, all affections associated with autoimmune processes.

Several mechanisms have been postulated to explain these spontaneous activities: epiphaptic excitation, hyperexcitability of peripheral ganglia, motor axonal atrophy and neuromuscular junction disorders. The results of Sinha et al suggest that "an increase in neurotransmitter release might result from an antibody mediated reduction in the number of potassium channels that normally regulate nerve excitability." Although carbamazepine (or phenytoin) remains the classic treatment for Isaacs' syndrome, a new therapeutic approach could be represented by immunomodulation: plasma exchanges, or immunosuppressors such as corticosteroids or azathioprine. Newsom-Davis et al used azathioprine in three cases, but always in association both with corticoids or plasma exchange, and with carbamazepine or phenytoin. In one case, only plasma exchanges were of temporary efficacy; the two other patients had at six and 18 months with prednisolone and azathioprine. Our patient also improved, albeit incompletely, with azathioprine as a sole treatment, and is now in a complex, complete disappearance of EMG patterns of neuromyotonia. A peculiar feature of this syndrome is the possibility of full recovery in the absence of underlying neuropathy, but this should be exceptional, after several years of carbamazepine or phenytoin treatment. Moreover, the sural nerve biopsy in our patient showed pathological changes.

Improvement could therefore probably be attributed to azathioprine.

Among their five patients, Newsom-Davis et al report the finding of antithyroid antibody in one, and a history of vasculitis in another. In three patients, there was an IgG intrathecal synthesis with oligoclonal profile, as in the patient of Elalaoui-Faris et al. We did not find any biological autoimmune abnormality in our patient and CSF analysis was normal. No CT of the thymus was undertaken. Nevertheless, coincidence with insulin dependent diabetes could be a stigma of an autoimmune process.

G RICHET P TROULLIAS
Service de Neurologie B
B ADY
Service d'Electromyographie, Hopital Neurologique,
59 Boulevard Fetal 69003, Lyon, France

Correspondence to: Professor P Trouillas, Service de Neurologie B, 59 Bd Penal, 69003 Lyon, France.


Hypomania after temporal lobectomy: a sequel to the increased excitability of the residual temporal lobe?

The occurrence of frank psychiatric illness after surgery has been a neglected topic until recently. It was not until the 1980s that a literature search showed scattered reports confirming the presence of overt psychoses, paraesthesiae, and personality changes. Here, we report a case of transient hypomania after temporal lobectomy for longstanding intractable complex partial seizures.

A 33 year old man with a history of rare generalised tonic-clonic seizures and intractable complex partial seizures since the age of 9 was admitted to our seizure monitoring unit for presurgical evaluation before temporal lobectomy. Brain MRI disclosed slight atrophy of the right hippocampus and interictal scalp EEG showed frequent right anterior temporal spikes. Because four ictal records of complex partial seizures with scalp EEG inclusive of sphenoidal electrode failed to provide definitive evidence of the side of origin of the seizures, depth electrodes, together with right sided subdural electrodes, were inserted. During the depth EEG study, four complex partial seizures and six simple partial seizures occurring as epigastric sensations were recorded. They were typical of the patient's habitual attacks. All of the 10
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G Riche, P Trouillas and B Bady

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