LETTERS TO THE EDITOR

Improvement of Isaacs’ syndrome after treatment with azathioprine

In Isaacs’ syndrome, muscular cramps exacerbated by effort, stiffness, delay in muscle degeneration, myokymia, fasciculations, and excessive perspiration are associated with spontaneous repetitive electromyographic discharges. The peripheral origin of the neuromyotonic discharge has been accepted since Isaacs’ first description,1 but the exact aetiology remains obscure.2

Sinha et al reported experimental arguments for an autoimmune process leading to quantitative reduction of the potassium channels on the axonal membrane.3 Three patients were identified from a clinic exchange;2,3 and three from azathioprine.4 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. These were abolished by tendon reflexes and palmar and plantar dystaesiae. Myokymia was seen in the interosseus 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, phosphate, magnesium, enzymes, blood count, serum immunoglobulin concentrations, thyroid function tests, cortisol concentration AbA1c, tumour markers. Serological tests for HIV, CMV, EBV, hepatitis A, B, and C, Borelia burgdorferi, echo, coxsackie, influenza, and parainfluenza were negative. IgG antibodies to HHV1, VZV, and measles were weakly positive. Tests for autoantibodies were negative including antinuclear, anti-DNA, antinuclear body test, antinuclear antibodies, muscle antibody, antimitochondrial antibodies, antinuclear antibodies, and antinuclear antibodies. Antibodies to HHV1 and HHV2 were positive. The patient was negative for hepatitis B and C antibodies. The patient was negative for hepatitis B and C antibodies.

The diagnosis of Isaacs’ syndrome was made and treatment was begun with carbamazepine. A dramatic reduction in nerve conduction velocity was noted in the next day and duration of neuromyotonic discharges decreased. In parallel, clinical improvement was notable. The patient was discharged after a few days because of cutaneous allergic reaction. Phenyltoin 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, pain and fungal fungation disappeared. Hyperhidrosis persisted, as well as some degree of neuromyotonia. An EMG in December 1991 showed improvement with persistence of neuromyotonic bursts only in the arms. The patient was discharged 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. Cramps persisted in the feet. Episodic diplopia had disappeared.

Since the initial two cases described by Isaacs,1 some 40 cases have been reported under various terms including neuromyotonia pseudoneuromyotonia, and muscle fibre activity. This syndrome has been described in association with polyradiculoneuropathy, peroneal small cell cencer, and thymoma, all affections associated with autoimmune processes.

Several mechanisms have been postulated to explain these spontaneous activities: ephaptic excitation, hyperexcitability of peripheral nerve, or motor axon-plexus 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.5 Although carbamazepine (or phenytoin) remains the classic treatment for Isaacs’ syndrome, a new therapeutic approach could be represented by immuno-modulation plasma exchanges.6 or immunosuppressors such as corticosteroids or azathioprine. Newsom-Davis et al used azathioprine in three cases,7 but always in association both with corticoids or plasma exchange, and with carbamazepine or phenytoin. In our case, only plasma exchanges were of temporary efficacy; the two other patients lasted six and 18 months with prednisolone and azathioprine. Our patient also improved, albeit incompletely, with azathioprine as a sole treatment, and azathioprine and prednisolone. 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 observed 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 six patients, Newsom-Davis et al report the finding of antihistidin antibody in one, and a history of vasculitis in another.1 In three patients, there was an IgG intrathecal synthesis with oligoclonal proteins, and the patient of Park-Faris et al.2 We did not find any biological autoimmune abnormality in our patient and CSF analysis was normal. No CT of the thymus was undertaken. Newsom-Davis et al concluded with insulin dependent diabetes could be a stigma of an autoimmune process.

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Hypomania after temporal lobectomy: a sequela 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 psychopathology after temporal lobectomy, resulting from a phenomenon of excitation of the remaining temporal lobe, arising for the first time after operation.1 The description of postoperative hypomanic states was even more difficult to find. Until recently, workers agreed that hypomania was non-existent, and that the occurrence of hypomanias was usually rare not among new psychoses after temporal lobectomy but also among epileptic psychoses in general.2 Here, I 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 a frequent right anterior temporal spikes. Because four ictal records of complex partial seizures with scalp EEG inclusive of sphenoidal electrodes 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
Machado-Joseph disease as the genetic basis of most spinocerebellar ataxias in Germany

Machado-Joseph disease is an autosomal dominant inherited neurodegenerative disorder pathologically characterised by regional loss of neurons in the cerebellum (especially the dentate nucleus), the spinal cord (spinocerebellar tracts, anterior horn cells, posterior columns, and Clarke's columns) and to varying degrees in the substantia nigra, the subthalamic nucleus, cranial motor nuclei, and peripheral nerves. Clinically Machado-Joseph disease presents with a broad range of symptoms including variable combinations of cerebellar ataxia, pyramidal and extrapyramidal features, peripheral neuropathy, progressive external ophthalmoplegia, and facioinguinal fasciculation. Machado-Joseph disease was originally described in Portuguese-Azorean families and has rarely been encountered in ethnic groups other than Portuguese. Up to now, no patients with the clinicopathological diagnosis of Machado-Joseph disease have been reported in Germany. Recently, the Machado-Joseph disease gene locus has been mapped to chromosome 14q and the disease causing mutation has been identified as an unstable and expanded (CAG) trinucleotide repeat. We investigated the Machado-Joseph disease mutation in 38 families with dominant cerebellar ataxias and in 21 patients with sporadic forms of ataxia of German ancestry. In 19 of 38 families an expanded trinucleotide repeat in the Machado-Joseph disease gene has been identified. Analysis of the (CAG), repeat length and the age of onset disclosed an inverse correlation, with the longest repeats in patients with juvenile onset (figure). None of the sporadic patients carried the Machado-Joseph disease mutation indicating that new mutations occur rarely. Prominent clinical features of the German patients with ataxia and bearing the Machado-Joseph disease mutation (table) included cerebellar symptoms such as ataxia of limbs, gait, and stance, dysarthria, and cerebellar oculomotor disturbances, and a varying combination of dysphagia, spasticity, and peripheral neuropathy with amyotrophy and sensory loss. Characteristic signs of Machado-Joseph disease as described in patients of Portuguese or Japanese descent, such as dystonia, extrapyramidal rigidity, faciolinguinal fasciculation, and auras of dysarthria, are rarely encountered.

**Clinical characteristics of patients with (SCA3), (MJD), and (SCA1)**

<table>
<thead>
<tr>
<th>SCAG/MJD Germany</th>
<th>MJD USA</th>
<th>MJD Japan*</th>
<th>SCA3</th>
<th>SCA1</th>
<th>Germany*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of families</td>
<td>19</td>
<td>7</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>No of patients</td>
<td>30</td>
<td>25</td>
<td>12</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Age of onset (mean (SD))</td>
<td>(years)</td>
<td>16 (17)</td>
<td>19 (31)</td>
<td>30 (13)</td>
<td>37 (34)</td>
</tr>
<tr>
<td>Range (SD)</td>
<td>19-51</td>
<td>10-64</td>
<td>20-44</td>
<td>20-47</td>
<td>32-47</td>
</tr>
<tr>
<td>Disease duration (mean (SD))</td>
<td>(years)</td>
<td>12 (5)</td>
<td>17 (11)</td>
<td>5 (10)</td>
<td>6 (8)</td>
</tr>
</tbody>
</table>

**Clinical signs:**
- Cerebellum: gait ataxia
- Limb ataxia and dysmetria
- Dysarthria
- Cerebellar ocular motor signs
- Pyramidal: spasticity
- Hyperreflexia
- Increased tendon reflexes
- Extensor plantar responses
- Extrapyramidal: rigidity
- Dystonia
- Atrophy
- Ophthalmoplegia
- Facioinguinal fasciculation
- Dysphagia
- Dementia

Correlation between the expanded (CAG) repeat length in the Machado-Joseph disease gene and the age of onset in patients with spinocerebellar ataxia type 3/Machado-Joseph disease. The regression curve derives from the formula: trinucleotide size = 63 ± 0.3 × age of onset (r = 0.79; P < 0.00000052).