Movement disorder associated with abnormal copper metabolism and decreased blood antioxidants

Sir: Dystonia not due to Wilson’s disease sometimes occurs in association with abnormal copper metabolism. The copper metabolism abnormalities are similar to those found in heterozygotes for the Wilson’s gene but the majority of these subjects are clearly asymptomatic. Other factors which may make patients unusually sensitive to minor disturbances of copper metabolism are not known. Increased tissue levels of transition metal ions are known to exert an increased pro-oxidant effect resulting in a greater tendency to membrane lipid damage and catecholamine oxidation. Moreover, such mechanisms are increasingly regarded as important in extrapyramidal disorders.

The normal defence against such oxidation is provided by a range of antioxidants of which glutathione is an important intracellular one. We describe a patient with a dystonic movement disorder who was found to have low serum copper, increased liver copper and decreased erythrocyte glutathione levels. We suggest that the combination of the copper and glutathione abnormalities may have resulted in dystonia when either on its own may have been insufficient to cause symptoms.

A 15 year old Indian schoolboy presented with a 3 year history suggestive of intellectual deterioration which improved spontaneously while undergoing investigation and a 1 year history of persistent and progressive abnormal movements and posture. During this year he had lost 6 kg in weight. He was not taking any drugs and in particular had never taken phenothiazines or other antipsychaminergic medication. There were no abnormal vocalisations or any obsessive compulsive behaviour. There was no family history of neuropsychiatric disorder or consanguinity, and perinatal and developmental history were normal. Examination showed tics of the face with frequent grimacing and to a lesser extent also involving his neck. His knees, right elbow and spine were held in partial flexion, the right shoulder semi-abducted and there was occasional dystonic posturing of the right hand. Gait was abnormally rapid and long stepped with some propulsion and during walking his right arm was held rigid at the shoulder with resulting decreased arm swing. Formal testing of mental function was within normal limits and there were no other neurological signs. No Kayser Fleischer rings were seen on slit lamp examinations done twice by an experienced ophthalmologist.

The results of the following blood tests were normal: blood count, erythrocyte sedimentation rate, serum urea, electrolytes, bilirubin, liver enzymes, proteins including immunoglobulins, calcium and tryponeural serology, serum transferrin, ascorbate, dehydroascorbate and products of lipid peroxidation in serum measured as diene conjugates and as thiobarbituric acid reactivity. CSF copper as measured by atomic absorption spectrophotometry and by its pro-oxidant potential was found to be normal. In addition, chest radiograph, CT scan of the head, electroencephalograph, isotope scans of the liver and spleen and CSF microscopy and protein content were normal. Serum copper was marginally low, as was serum caeruloplasmin. Liver copper measured by atomic absorption spectrophotometry was raised but not to the levels normally accepted for Wilson’s disease. Red cell reduced glutathione measured by the method of Crowley et al was low. This method is in regular use in our laboratory where the normal ranges quoted have been established. These are in good agreement with normal ranges reported by other groups. These findings are summarised in the table. His parents’ serum copper and caeruloplasmin were measured and were found to lie well within normal limits.

Although patients with neurological problems due to Wilson’s disease who have no Kayser Fleischer rings have very rarely been described our patient cannot be regarded as coming within this category. The modest elevation in liver copper with normal histology, normal urine copper levels and low serum copper and caeruloplasmin might all individually occur in classical Wilson’s disease but taken together they are not acceptable for that diagnosis.

Caeruloplasmin is the main anti-oxidant in human plasma and glutathione an important one within cells where it is known to play a role in membrane stabilisation and in providing a suitable reducing environment. When levels of one antioxidant are decreased the functional demands on other antioxidants are increased. Marginal lowering of serum caeruloplasmin along with significant lowering of intracellular glutathione may together have resulted in decreased antioxidant protection both in cells and in serum. In vitro low levels of glutathione in the presence of metal ions increase the risk of free radical mediated oxidative damage. Thus, decreased levels of glutathione along with increased tissue copper may be especially harmful. It seems unlikely that the glutathione deficiency is a consequence of increased glutathione consumption as in that case levels of all antioxidants should be low, which is not true for ascorbate and also levels of serum lipid peroxidation products are within normal limits.

There are reports in the literature of abnormalities suggestive of heterozygous state for the Wilson’s disease allele association with extrapyramidal dysfunction. This may be the explanation in our patient although the fact that both his parents’ serum caeruloplasmin concentrations are entirely normal is against this. It is equally possible that Wilson’s disease is not a single entity and that patients such as we describe will prove genetically distinct from classical Wilson’s disease. Penicillamine which is the drug of choice in the treatment of Wilson’s disease.

Table Results of copper and glutathione studies

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal range</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum copper</td>
<td>0.5 mg/l</td>
<td>0.7–1.6</td>
<td>Atomic absorption spectrophotometry (AAS)</td>
</tr>
<tr>
<td>Serum caeruloplasmin</td>
<td>0.15 g/l</td>
<td>0.2–0.6</td>
<td>Immunoassay</td>
</tr>
<tr>
<td>Basal urine copper excretion</td>
<td>450 mg/l</td>
<td>480–840</td>
<td>Ferroxidase activity</td>
</tr>
<tr>
<td>Liver copper concentration</td>
<td>15 µg/24 hours</td>
<td>&lt; 70</td>
<td>AAS (Addenbrooke’s Hospital Cambridge)</td>
</tr>
<tr>
<td>Whole blood glutathione</td>
<td>106 µg/ml</td>
<td>&gt; 280</td>
<td>(Reference 6)</td>
</tr>
<tr>
<td></td>
<td>24 mg GSH/10⁰²</td>
<td>&gt; 80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Red Cells</td>
<td>40–90</td>
<td></td>
</tr>
</tbody>
</table>
Letters

disease has been said to increase intracellular glutathione levels as well as chelating copper and for both these reasons we are considering penicillamine therapy in our patient.

References

5. Gutteridge JMC. Copper phenanthroline induced site specific oxygen-radical damage to DNA. Detection of loosely bound trace copper in biological fluids. Biochem J 1984;218:983-5.

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Ocular flutter, postural body tremulousness and CSF pleocytosis: a rare post-infectious syndrome

Sir: The neurological sequelae of non-specific febrile illnesses include meningoencephalitis, myelitis and polyradiculitis. A rare, distinctive post-infectious syndrome comprising ocular flutter, body tremulousness and cerebrospinal fluid (CSF) pleocytosis has been described.1-3 Outcome is favourable but the infectious agent and pathophysiology remain uncertain.

Three weeks prior to presentation a 31 year old man, accustomed to jogging 6 km per day, found himself unusually short of breath whilst running and experienced generalised myalgia, arthralgia and headache. One week later he developed an unsteady gait and became nauseated. When sitting or standing his trunk and limbs felt jittery and shaky. Sudden loud noises precipitated brief shock-like jerks of the limbs and trunk. His symptoms improved over the following week but subsequently recurred, prompting his admission.

On examination he was afebrile and abnormal findings were confined to the nervous system. Initially he was noted to have horizontal gaze-evoked nystagmus but after a few days ocular examination revealed sudden bursts of conjunctival horizontal saccadic oscillations without intersaccadic interval (ocular flutter) occurring both spontaneously and with fixation, with eyes open and closed, during pursuit and saccades, and in all direction of gaze (fig). Downgaze was particularly provocative. The ocular excursion was full and optokinetic responses were normal bilaterally. When lying in bed limb ataxia was minimal and there were no involuntary movements. However, on standing, irregular jerks of the head, trunk and limbs were present. Standing on either leg accentuated the truncal tremulousness which was difficult to characterise. Anxiety, chorea, myoclonus and truncal ataxia were all considered by different examiners. This absence of involuntary movements when lying contrasted with the disorder seen when assuming the upright posture. Palatal myoclonus was not observed.

Cerebrospinal fluid (CSF) examination revealed 8 lymphocytes per µl, protein 0.28 g/l (normal 0.15-0.45), glucose 3.9 mmol/l (normal 2.8-4.4) and IgG/albumin ratio 0.24 (normal 0.04-0.24).

Electrocardiograph showed first degree heart block and anterolateral T wave inversion. Electroencephalograph was normal but irregular eye movement artefact was present throughout the recording, more obvious with the eyes closed, and suggestive of ocular flutter or opsoclonus. Attempted

Fig Electro-oculography, looking down. Burst of conjugate horizontal saccadic oscillations without intersaccadic interval (ocular flutter).

Right eye

Left eye

T3-C3

Looking down

FP2

FP1

T4-C4

FP1-F3

FP2-F4

300 microvolts

200 milliseconds

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