Restless legs syndrome and low brain iron levels in patients with haemochromatosis

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Regional brain iron levels of two patients with haemochromatosis and severe restless legs syndrome (RLS) were assessed using R2* magnetic resonance imaging (MRI) sequences in both patients and in nine healthy controls. R2* relaxation rates in the patients were decreased in the substantia nigra, red nucleus, and pallidum when compared with the controls. These results indicate that local brain iron deficiency may occur in patients with haemochromatosis and suggest a role for brain iron metabolism in the pathophysiology of RLS.

At the origin of her insomnia was a compelling urge to move the limbs, usually associated with leg discomfort that the patient described “like electric current”. These symptoms were exclusively present at rest, beginning after a delay of several minutes after the patient lay down and interfering with sleep onset. She had tried several hypnotics without lasting success.

Polysomnography demonstrated the presence of PLMS (index = 21.5 movements/hour of sleep), mostly associated with micro arousals. Routine laboratory analysis to rule out secondary RLS showed increased level of serum ferritin (305 ng/dl) and serum transferrin saturation (88%). Detailed biochemical investigations were done with the genotyping of the HFE gene, which showed homozygous C282Y mutation.

Clinically, the patient had no other organ manifestations. She was treated by venesection (initially twice a month, then once every three months), but there was no improvement in the sleep complaints. Clonazepam was then introduced, which diminished the RLS related symptoms and the associated insomnia.

She was not aware of RLS or any other case of haemochromatosis in her family. Her only brother was subsequently screened for haemochromatosis, and he was also homozygous for C282Y.

Patient 2

A 56 year old man was diagnosed as having haemochromatosis at the age of 53 years. Non-specific presenting symptoms (such as weakness, fatigue, apathy, and lack of libido) had appeared progressively approximately 18 months before the diagnosis. At that time, there were no significant clinical findings on the physical examination and the patient had no noteworthy medical or surgical history except for an episode of renal calculus 20 years previously. The patient was finally referred to the department of internal medicine of an academic hospital on the basis of an unexplained high level of blood ferritin, incidentally found on an extensive blood analysis. He was diagnosed as having hereditary haemochromatosis by a liver biopsy showing iron overload and a homozygous C282Y mutation on genotyping. The patient was not able to identify retrospectively any other case of haemochromatosis in his family.

Three years later, the patient was referred to our sleep disorder centre for a complaint of insomnia, non-restorative sleep, and daytime fatigue despite a regular phlebotomy regimen (that is, removal of 350 ml of whole blood every two weeks). Typical symptoms of RLS with paraesthesia and dysesthesia in the legs relieved by movement were evidenced. The phlebotomies seemed to increase temporarily the brain iron levels, which were exclusively present at rest, beginning after a delay of several minutes after the patient lay down and interfering with sleep onset. She had tried several hypnotics without lasting success.

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CASE REPORTS

Patient 1

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As regards RLS, we can only postulate that our patients represent sporadic associations between the two illnesses, in particular considering the elevated prevalence rates reported in the literature for RLS (ranging between 4% and 15%). But our MRI findings, similar to those reported by Allen et al in idiopathic RLS, indicate a possible role of local brain iron deficiency in the pathophysiology of RLS and PLMS, even in patients with systemic iron overload, such as in our patients. The discrepancy between serum and brain iron levels in patients with RLS further indicates that symptoms are not linked to low serum iron levels but to low regional brain iron availability. An alteration in the blood–brain barrier iron transport mechanism may be implicated in the pathophysiology of RLS symptoms. Further studies, analysing CSF ferritin and transferrin, and brain iron levels, are needed to confirm the hypothesis that an abnormal brain iron level is a primary mechanism of RLS.

Table 1

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>Median R2' (1/msec)</th>
<th>Range</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n = 9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substantia nigra</td>
<td>0.0105</td>
<td>0.0059-0.0198</td>
<td>0.0037</td>
<td>0.0043</td>
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<tr>
<td>Putamen</td>
<td>0.0094</td>
<td>0.0077-0.0149</td>
<td>0.0102</td>
<td>0.0110</td>
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<tr>
<td>Caudate</td>
<td>0.0135</td>
<td>0.0066-0.0258</td>
<td>0.0080</td>
<td>0.00284</td>
</tr>
<tr>
<td>Pallidum</td>
<td>0.0095</td>
<td>0.0077-0.0184</td>
<td>0.0066</td>
<td>0.0052</td>
</tr>
</tbody>
</table>

**Assessment of brain iron levels with MRI**

After obtaining written informed consent, we assessed the regional brain iron levels in both patients using a whole body 3 Tesla MRI system (Medspec S300, Brucker Medical, Germany). The MRI was done shortly after the polysomnographic recordings (15 days and two days, respectively). Effective transverse relaxation rates (R2') were measured in different brain regions of interest (ROI) using a hybrid sequence combining one spin echo with 16 gradient echoes (Fig 1). A set of 10 slices of 5 mm thickness and 1×2 resolution was acquired. R2' sequences have been shown to be an accurate, indirect, and quantitative non-invasive measure of brain iron levels. The results were compared with those from a group of nine healthy volunteers (five men, four women; mean (SD) age 48.1 (8.7) years, range 36–65) with no symptoms of RLS or primary sleep disorder, as assessed by polysomnography. R2' values were substantially decreased in the substantia nigra, red nucleus and pallidum in both patients compared with the controls (table 1), suggesting an iron deficit in these regions in the patients. These findings reveal that local brain iron deficiency may occur in patients with haemochromatosis, as if the blood–brain barrier is able to restrict the transport of the excess plasma iron to the brain.

**REFERENCES**