Relapsing encephalopathy with dancing eyes and jerky limbs

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ABSTRACT

We report a case of relapsing-remitting opsoclonus-myoclonus-ataxia syndrome (OMAS) in a patient with Hashimoto's encephalopathy, diagnosed after comprehensive evaluation. OMAS as a manifestation of Hashimoto's encephalopathy has been reported once previously. It is hoped that recognition of this entity and early initiation of immunotherapy will improve clinical outcomes for patients.

A 50-year-old Indian woman presented with a four-month history of unsteadiness, reduced speech and jerky movements, worsening over two weeks. She had a background history of two steroid-responsive neurological episodes, characterized by tremor and incoordination, and bilateral leg weakness, thirteen and two years prior, respectively. She was managed in outside hospitals and recovered fully with no long-term immunotherapy.

On examination, she was febrile and obtunded. There were involuntary, chaotic, rapid and multi-directional conjugate saccadic eye movements associated with stimulus-sensitive, brief, shock-like involuntary movements in the upper limbs, consistent with opsoclonus and myoclonus, respectively (Video Segment 1). She was subsequently intubated because of respiratory distress and reduced conscious state. Laboratory evaluations revealed pancytopenia and elevated liver enzymes as complications of sepsis secondary to pneumonia. Brain MRI showed lesions in cortical and subcortical regions, pons and midbrain (Fig. 1). Electroencephalogram (EEG) demonstrated diffuse slowing without epileptiform discharges. Investigations for other sources of infectious, autoimmune and neoplastic disorders were negative (Supplementary Table). The opsoclonus-myoclonus-ataxia syndrome (OMAS) was presumed to be parainfectious in origin. She recovered over three months with empirical antibiotics without receiving immunotherapy.

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She remained well until three years later when she represented with opsoclonus, myoclonus and emotional lability, preceded by a two-month history of irritability and gait instability. She was confused and fearful, with opsoclonus and stimulus-sensitive myoclonus in both upper limbs (Video Segment 2). Brain MRI demonstrated similar lesions as before, but without contrast enhancement. Brain MR angiogram and spinal MRI were normal. Cerebrospinal fluid (CSF) examination revealed mild lymphocytic pleocytosis and intrathecal IgG synthesis with oligoclonal band. EEG was diffusely slow. Surface electromyography of limb muscles showed irregular, short electromyographic bursts of 100–200 ms, consistent with myoclonus. Additional tests were performed during this admission. Anti-thyroid peroxidase (TPO) antibody was significantly elevated (632 IU/mL) with normal anti-thyroglobulin (TG) antibody titer (28.5 IU/mL). Thyroid-stimulating hormone was low with normal free T3 and T4, indicating subclinical hyperthyroidism. Extensive evaluations for infectious, autoimmune and neoplastic disorders were unrevealing (Supplementary Table).

The patient was diagnosed with Hashimoto's encephalopathy (HE) according to the Graus criteria [1] and treated with intravenous methylprednisolone (1 g/day for five days), resulting in improvement of her mental state, opsoclonus and myoclonus; the EEG normalized and anti-TPO antibody titer reduced substantially (181 IU/mL). However, as the patient remained emotionally labile with ataxic gait four weeks post-treatment, plasmapheresis was administered over five days. This resulted in resolution of the opsoclonus and myoclonus, and she became more conversant and started to ambulate. Anti-TPO antibody titer further reduced to 47.7 IU/mL. Brain MRI three weeks after
plasmapheresis showed slight improvement of the periventricular lesions. She was discharged home with a slow prednisolone taper. At follow-up five months later, the patient had returned to her baseline mental state, but remained mildly ataxic.

HE, also known as steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), remains an enigmatic entity, with heterogeneous features that can include mental state changes, seizures, aphasia and stroke-like episodes [1,2]. The most commonly reported movement disorders associated with HE are myoclonus (37–65%), tremor (28–84%) and ataxia or gait disturbance (28–65%) [2]. A variety of other movement disorders have also been described (Table 1) [3–13]. HE diagnosis requires the presence of encephalopathy with exclusion of well-characterized neuronal antibodies and other reasonable causes [1]. Thyroid autoantibodies are thought to be an autoimmune epiphenomenon rather than being directly pathogenic. Their use as a marker for disease activity remains controversial, as some authors reported no correlation between antibody level and clinical severity [2]. In HE, thyroid function and other laboratory and neuroimaging findings are usually normal or non-specific; therefore, a high index of suspicion is needed. “Red flags” that prompted testing for thyroid antibodies in our patient were the encephalopathy and history of relapsing-remitting neurological presentations. Despite encephalopathy typically being a main feature, patients can present with movement disorders without mental impairment (Table 1).

OMAS is rare and has been associated most commonly with parainfectious or paraneoplastic causes [14], with isolated cases of non-parainfectious/non-paraneoplastic associations also reported [15]. To our knowledge, OMAS as a manifestation of HE has been reported in a single case previously [3]. Isolated opsoclonus or ataxia have also been reported, presumably representing formes frustes of the full-blown syndrome [4,16]. One novel aspect of our case was the relapsing-remitting nature of the OMAS, which has not been reported in HE. In two series of adult-OMAS [14,17], four patients with idiopathic OMAS had early relapse, within the first month to one year of treatment. We found no adult-OMAS relapsing after a prolonged remission as in the present case. Our patient also had neuroimaging lesions that appeared to include the paramedian pontine reticular formation (PPRF), a structure implicated in the pathogenesis of opsoclonus, in which spontaneous activity of saccadic burst cells is “released” from inhibition by pontine pause cells [18]. We note however that in most reported cases of OMAS, and specifically in the two previous reports of opsoclonus in HE, no MRI brainstem lesions were demonstrable [3,4,14].

Similar to HE, the exact pathophysiology underlying OMAS remains to be fully elucidated but the presence of autoantibodies, oligoclonal bands in the CSF, and response to immunotherapies in the majority of OMAS cases support immune-mediated mechanisms. In cases of
<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Age/Sex</th>
<th>Movement Disorder</th>
<th>Other Neurologic Features</th>
<th>Immunotherapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hernández Echebarría (2000)</td>
<td>3/</td>
<td>Opsoclonus, myoclonus, gait anesthesia,ataxia, tremor</td>
<td>Seizures, irritability, paranoid ideation, insomnia, mutism, memory loss, altered mental state</td>
<td>± Hyperthyroid (overt)</td>
<td>Back to baseline after treatment</td>
</tr>
<tr>
<td>Lee (2015)</td>
<td>30/M</td>
<td>Ocular flutter, limb and gait ataxia, myoclonus, tremor</td>
<td>Dysarthria</td>
<td>+ Normal</td>
<td>Back to baseline 3 months after treatment</td>
</tr>
<tr>
<td>Erickson (2002)</td>
<td>6/</td>
<td>Myorhythmia, myoclonus, tremor</td>
<td>Stupor, agitation, seizures</td>
<td>+ Hypothyroid (overt)</td>
<td>Moderate improvement with residual mild cognitive impairment and subtle focal myopathy; then PO prednisone taper over 1 year</td>
</tr>
<tr>
<td>Keshavarz (2018)</td>
<td>23/F</td>
<td>Orolingual dyskinesia</td>
<td>Excessive talking, emotional lability</td>
<td>+ Normal</td>
<td>Significant improvement 8 weeks after treatment</td>
</tr>
<tr>
<td>Liu (2012)</td>
<td>75/M</td>
<td>Paroxysmal kinesigenic dyskinesia</td>
<td>Cognitive impairment, speech difficulty</td>
<td>+ Normal</td>
<td>Back to baseline 20 days after treatment</td>
</tr>
<tr>
<td>Nakpal (2004)</td>
<td>52/F</td>
<td>Parkinsonism, myoclonus</td>
<td>Cognitive impairment, aphasia</td>
<td>+ Normal</td>
<td>No improvement with IVMP; significant improvement 10 days after IVMP</td>
</tr>
<tr>
<td>Inoue (2012)</td>
<td>63/F</td>
<td>Parkinsonian gait, tremor</td>
<td>Cerebral atrophy</td>
<td>+ Normal</td>
<td>Moderate improvement after 2 weeks</td>
</tr>
<tr>
<td>Rožanković (2015)</td>
<td>27/F</td>
<td>Myoclonus-dystonia, choreoathetosis, gait ataxia</td>
<td>Headaches</td>
<td>+ Normal</td>
<td>No improvement with IVMP; significant improvement 10 days after IVMP</td>
</tr>
<tr>
<td>Miranda (2018)</td>
<td>61/M</td>
<td>Hemidystonia, myoclonus, gait ataxia</td>
<td>Dysarthria</td>
<td>+ Normal</td>
<td>Mild improvement only after ramifluoxetine</td>
</tr>
</tbody>
</table>

Abbreviations: M: male; F: female; anti-TPO: anti-thyroid peroxidase; anti-TG: anti-thyroglobulin; ↑: elevated; CSF: cerebrospinal fluid; MRI: magnetic resonance imaging; +: present; <: absent; n.r.: not reported; R.R.: reference range; IV: intravenous; MP: methylprednisolone; IG: immunoglobulin; PO: oral.
insufficient response to corticosteroid treatment, further improvement is possible with plasmapheresis or intravenous immunoglobulin [14], as exemplified by our patient. The missed diagnosis of HE during her first OMAS presentation and treatment delay could be a contributing factor for the patient’s relapse and incomplete steroid response. We hope that awareness of HE as a cause for OMAS will aid earlier recognition and initiation of treatment, which may be critical for optimal outcomes in these patients.

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Conflicts of interest

All authors declare that there are no conflicts of interest relevant to this work.

Ethical compliance and consent

We confirm that the approval of an institutional review board was not required for this work. Written informed consent for publication of this case report and video has been obtained from the patient.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.02.025.

References