Autonomic alterations as a clinical manifestation of encephalopathy associated with autoimmune thyroid disease

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Abstract. Encephalopathy associated with autoimmune thyroid disease (EAATD), also known as Hashimoto’s encephalopathy, is a rare neurological condition that may occur in patients with clinical or sub-clinical autoimmune thyroid disease. The pathogenesis of EAATD has been not clearly elucidated yet. The diagnostic criteria include neurological or psychiatric symptoms, high levels of anti-thyroid antibodies, and exclusion of other possible causes of encephalopathy. In the large majority of cases, EAATD patients respond to immunosuppressant therapies, in particular to corticosteroids. We report the case of a patient with Hashimoto’s thyroiditis and recurrent manifestations of encephalopathy over the previous few years responding to corticosteroid treatment. The patient presented with language and cognitive impairment, ataxia, and neurovegetative/autonomic symptoms. She was euthyroid with mildly raised anti-thyroid peroxidase antibodies. An extensive diagnostic work-up, including electroencephalogram, brain magnetic resonance, hormonal assessment, and an exhaustive panel of antibodies possibly associated with autoimmune encephalopathy, was carried out and excluded other possible etiologies of encephalopathy. The diagnosis of EAATD possibly affecting the hypothalamus and/or the neurovegetative regulatory centers was made and treatment with prednisolone was timely commenced with a dramatic and rapid improvement with progressive normalization of the symptoms. To the best of our knowledge, this is the first report of neurovegetative/autonomic alterations in the setting of EAATD.

Key words: Autoimmune thyroid disease, Hashimoto’s thyroiditis, Encephalopathy, Neurovegetative symptoms

ENCEPHALOPATHY associated with autoimmune thyroid disease (EAATD), also known as Hashimoto’s encephalopathy, is a rare neurological condition that may affect patients with clinical or sub-clinical autoimmune thyroid disease [1, 2], most commonly Hashimoto’s thyroiditis [3], but it has been reported also in association with Graves’ disease [1, 4, 5]. The most frequent clinical manifestations include seizures, myoclonus, cognitive impairment, altered consciousness, ataxia, stroke-like focal deficits, psychiatric disorders, tremors, and behavioural changes [3, 6]. However, any neurological or psychiatric symptom can potentially occur in EAATD. The onset of EAATD may be acute or sub-acute, and the subsequent clinical course varies from progression of symptoms, recovery with reoccurrence, or complete recovery. Exceptionally, EAATD results in a fatal outcome [7, 8].

The clinical presentation is often subtle as the symptoms are non-specific. Thus, a correct diagnosis may be delayed [3, 9]. The diagnostic criteria are based on the association of neurological or psychiatric symptoms, the presence of anti-thyroid antibodies, the exclusion of...
other possible causes, and often a significant improvement with steroids or other immunosuppressants [3, 6, 9, 10]. Unfortunately, the obvious issues related with the attainment of a cerebral biopsy sample and the lack of a definitive laboratory diagnostic test or a revealing radiological investigation make the diagnosis of EAATD to be firstly a diagnosis of exclusion. Extensive investigations are required to rule out other possible causes of the neurological or psychiatric symptoms [11]. Patients presenting with EAATD often have normal or clinically insignificant abnormal thyroid hormone levels with evidence of anti-thyroid autoimmunity, in particular positive anti-thyroid peroxidase antibodies (anti-TPO Abs) in the serum and/or cerebrospinal fluid (CSF). Other markers of EAATD include increased CSF protein concentration, non-specific white matter changes on magnetic resonance (MR), and non-specific diffuse electroencephalogram (EEG) abnormalities [11, 12]. In recent times there has been a steady increase in the number of cases of EAATD described in the literature, at least partially due to increased awareness of this condition [13].

We describe the case of a patient presenting with neurovegetative/autonomic symptoms in the setting of EAATD. This case highlights once again the profound variability in the clinical presentation of EAATD, which still represents a diagnostic challenge both for the neurologist and the endocrinologist.

Case Report

A fifty-nine-year-old woman attended the emergency department of our hospital with recurrent falls and ataxia associated with speech impairment, poor concentration, and drowsiness. The patient and her family described a progressive deterioration in her condition over a period of two months, with most marked effects on speech and mobility. At the time of the admission, her speech was significantly slow and she was immobile due to severe ataxia. Regular medications were: levothyroxine, bumetanide, risperidone, calcium, vitamin D, denosumab, thiamine, folic acid, and levetiracetam. There was no history of recent acute or chronic infections or toxic exposure. Interestingly, in the previous four years the patient had a large number of admissions with various symptoms of encephalopathy, such as seizures, amnesia, dysarthria, ataxia, psychosis, and social withdrawal. During past admissions, an underlying etiology was not identified despite repeat CSF analysis, EEG, and MR. She was always euthyroid or subclinically hypothyroid.

Anti-TPO Abs were persistently positive, though usually less than ten times above the upper normal limit. On all of these occasions, her condition improved with steroids. The patient had a past medical history of Hashimoto’s thyroiditis, osteoporosis, and cataracts. She previously underwent a left thyroid lobectomy for a nodule suspicious at the ultrasound. However, the histology demonstrated only the presence of lymphocytic thyroiditis without any neoplastic findings.

On admission the patient was bradycardic (heart rate of 38–42 beats per minute, regular), hypotensive (100/40 mmHg), and hypothermic (34.2°C). Respiratory rate and oxygen saturation levels were within normal limits. She was drowsy, with markedly impaired concentration, comprehension, and speech. Neurological examination revealed absence of coarse deficits of the cranial nerves, there was no nuchal rigidity or photophobia. The assessment of the peripheral nervous system was limited due to her poor cooperation and impaired coordination. She was very unsteady on her feet with inability to mobilize and her balance was significantly affected. There were no abnormalities in reflexes, sensation, muscle power or tone. The remaining physical examination was unremarkable. Blood tests showed mild anaemia with haemoglobin 10 g/dL and thrombocytopenia with platelets 44 × 10^9/L. The remaining blood tests, including white cell count, electrolytes, coagulation, liver function, renal function, C-reactive protein, serum protein electrophoresis, vitamin B12, and folate acid, were in normal range. Thyroid function tests were normal with free thyroxine 18.3 pmol/L and thyroid stimulating hormone 2.19 mIU/L. Anti-TPO Abs were mildly elevated at 38.5 IU/mL (normal levels <5.6 IU/mL). Anti-NMDA receptor Abs, anti-VGKC Abs, and a panel of antibodies associated with paraneoplastic encephalopathy, including anti-Hu, anti-Yo, anti-Ri, anti-Ma1, and anti-Ma2, were all negative. Infective disease screening, including HIV and Treponema Pallidum, was negative.

Brain computed tomography (CT) was negative. Brain MR and MR angiogram revealed non-specific scattered punctate foci of T2 FLAIR hyper-intensity within the cerebral deep white matter, stable compared to previous studies and most likely consistent with a chronic small vessel disease (Fig. 1a). No relevant abnormalities were seen in the hypothalamic/pituitary region (Fig. 1b). EEG was abnormal in the awake, drowsy, and asleep state with diffuse background slowing with left side predominance. There was a profound absence of alpha rhythm throughout all studies (Fig. 2a), with lack of reactivity to
Fig. 1  a–b Brain MR showing non-specific scattered punctate foci of T2 FLAIR hyper-intensity (arrows) within the cerebral deep white matter, likely consistent with a chronic small vessel disease (Fig. 1a). The hypothalamic/pituitary region did not show any significant abnormality (Fig. 1b).

Fig. 2  a–b EEG record on EAATD onset showing an abnormal diffuse background slowing with left side predominance and absence of alpha rhythm (Fig. 2a). Six months later, the abnormal findings normalize while the patient was still on low dose corticosteroids (Fig. 2b).
eye opening. Transient fronto-temporal higher amplitude delta slow waves were observed, in particular in the drowsy state and predominant on the left side.

Primary or secondary hypocorticism was excluded on the basis of the clinical findings, the laboratory parameters, and did not match with the concomitant EEG abnormalities. Moreover, repeated assessment of the pituitary function and adrenal axis was carried out at the time of previous admissions and did not disclose any abnormality, including normal ACTH, cortisol, and sodium.

Since encephalopathy has many possible causes, including anoxia, infection, arterial hypertension, traumatic brain injury, liver failure, renal failure, intoxication, tumours, prion disease, and mitochondrial disorders, the differential diagnosis was very challenging. The investigative findings reported above ascribed this case to the group of immunomediated/inflammatory encephalopathies [14, 15]. Among them, EAATD should be considered given the diagnosis of an autoimmune thyroid disease in euthyroidism with positive anti-TPO Abs and with consistent EEG and MRI features. However, the most frequent causes of immunomediated/inflammatory encephalopathy had to be excluded. A primary cerebellar disorder was ruled out radiologically. Imaging, together with the complex of signs, symptoms, and other findings also excluded stroke, intracranial haemorrhage, multiple sclerosis, and space occupying lesions. There was no biochemical evidence of metabolic causes like hypoglycaemia, electrolyte imbalance, or vitamin deficiencies and there was no toxin or drug use and no history of head trauma. The history of the patient was not consistent with Creutzfeldt-Jakob disease (CJD), though such condition should be considered in any patient who presents with rapidly progressive neuropsychiatric symptoms. Finally, psychiatric conditions were also considered, however her history was not reflective of this and some clinical manifestations, namely hypothermia and bradycardia, were not consistent with a psychiatric pathology.

In this case, the patient history, clinical manifestations, and diagnostic findings enabled us to rule out safely other possible causes of encephalopathy and, in the setting of euthyroid Hashimoto’s thyroiditis with positive anti-TPO antibodies, EAATD was the most likely diagnosis. Given the diagnosis of EAATD, high-dose steroid treatment was commenced with prednisolone 80 mg once daily. A dramatic improvement of the symptoms occurred within the first twenty-four hours of treatment, a treatment response which further cemented the diagnosis. Two weeks later, the neurological and cognitive symptoms were completely resolved. In addition, the thrombocytopenia, which most likely was autoimmune in nature, resolved with steroid treatment. Three weeks after the admission, the patient was discharged on a tapering dose of steroids. During her inpatient admission, she received intensive physiotherapy input with a further improvement of gait and on discharge she was at baseline mobility. On discharge, her heart rate was 50 beats per minute, blood pressure 105/55 mmHg, and body temperature 35°C. Two months after the discharge from the hospital, she was reviewed in the outpatient clinic for follow-up. She was on a low maintenance dose of prednisolone (5 mg once daily). The patient was in good general condition, denied any recurrence of neurological symptoms or occurrence of new clinical issues. Her heart rate was 56 beats per minute, blood pressure 105/50 mmHg, and body temperature 35.1°C. As per the literature recommendations and given the satisfactory therapeutic response with good patient tolerability to steroid treatment, low-dose prednisolone was continued. Six months after the admission, while still on low maintenance dose prednisolone, her EEG appeared to have basically normalized (Fig. 2b). After eighteen months from that admission and four months after the steroids withdrawal, she was still asymptomatic and in excellent general conditions, including the persistence of normal vital parameters.

**Discussion**

EAATD still represents a controversial entity characterized by heterogeneous manifestations. It is a diagnosis of exclusion with diagnostic criteria based on the association of neurological or psychiatric symptoms, positive anti-thyroid antibodies, exclusion of other possible causes, and in most cases occurrence of a significant improvement of the symptoms with steroids or other immunosuppressants [3, 6, 9, 10]. The pathogenesis of EAATD is yet to be elucidated. Most authors consider this condition an immune-mediated inflammatory event affecting the central nervous system. An autoimmune process involving common brain-thyroid antigens or a cerebral vasculitis has been proposed as possible pathogenetic mechanisms [1, 3, 11, 16]. Moreover, antibodies against alpha-enolase which is present both in the thyroid and brain, have been detected in some patients [17, 18]. It was suggested that the variation in clinical presentation may reflect the global nature of autoimmune and vascul-
litic processes, with varying brain regions potentially involved [19].

EAATD patients show a wide variability in the clinical presentation, diagnostic findings, and sometimes also in the response to therapy [2, 6, 11]. The above described patient had longstanding history of relapsing EAATD with seizures, ataxia, speech impairment, and altered consciousness. At the time of admission, she presented with bradycardia, hypotension, and hypothermia. Not only did the neurological and cognitive symptoms dramatically resolve after the commencement of the steroid treatment, but also the autonomic findings significantly improved. The autonomic changes characterizing her clinical presentation and the subsequent improvement with steroids suggest that the hypothalamus and/or the neurovegetative regulatory centers were possibly affected. Paradoxically, the hypothermia significantly improved on high-dose steroids. To the best of our knowledge, no previous reports of neurovegetative/autonomic alterations have been ever described in EAATD. On the contrary, a few cases of bradycardia and hypothermia secondary to infectious or autoimmune hypothalamic or limbic encephalitis have been reported [20-23]. In particular, hypothermia and haemodynamic changes consistent with autonomic dysfunction have been observed in patients with anti-Ma-2 Abs, anti-NMDA receptor Abs, and anti-VGKC Abs, the latter targeting usually the hippocampus and the mesial temporal lobe [24, 25].

In regards to the diagnostic findings, EEG plays a relevant supportive role, though usually poorly specific [26]. Consistently with the most typical EAATD records [11, 27], the EEG of the above described patient showed diffuse background slowing and lack of reactivity to eye opening. There were also transient left fronto-temporal predominant delta slow waves [9, 10]. Brain imaging in EAATD is often non-specific, however it is crucial for the exclusion of other possible causes of the symptoms [11, 27]. In the largest systematic review available in the literature, up to 50% of patients had cerebral atrophy or infarct and/or focal cortical abnormalities, or evidence of unspecific focal or diffuse subcortical white matter changes [9, 11].

The differential diagnosis of EAATD is usually a relevant challenge since encephalopathy has many possible causes, including anoxia, infection, arterial hypertension, traumatic brain injury, liver failure, renal failure, intoxication, tumors, prion disease, and mitochondrial disorders [14]. The main differential diagnosis and diagnostic workup are detailed in Table 1. At first instance, the investigative findings reported above ascribed this case to the large and pleomorphic group of immunomediated/inflammatory encephalopathies [14, 15]. Among them, EAATD should be considered given the diagnosis of an autoimmune thyroid disease in euthyroidism with positive anti-TPO Abs and with consistent EEG and MR features. However, the most frequent causes of immunomediated/inflammatory encephalopathy have to be excluded first. A primary cerebellar disorder could account for poor coordination, ataxia, and recurrent falls however neuroimaging did not confirm radiologically evident cerebellar abnormalities and other neurological

<table>
<thead>
<tr>
<th>Cause of encephalopathy</th>
<th>Exclusion</th>
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<tbody>
<tr>
<td>Anoxia</td>
<td>No history of same</td>
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<tr>
<td>Infection</td>
<td>Normal CSF biochemical parameters, negative CSF culture, negative serum inflammatory markers</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Blood pressure below 140/90 mmHg</td>
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<tr>
<td>Chronic trauma</td>
<td>No history of same</td>
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<tr>
<td>Hepatic cirrhosis</td>
<td>Inconsistent clinical, biochemical, and radiological findings</td>
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<tr>
<td>Renal failure</td>
<td>Normal renal function</td>
</tr>
<tr>
<td>Intoxication</td>
<td>No history of same, no biochemical suggestion of same</td>
</tr>
<tr>
<td>Prion disease including CJD</td>
<td>No element of dementia, inconsistent MR and EEG findings, negative CSF 14-3-3 protein</td>
</tr>
<tr>
<td>Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome</td>
<td>No history of stroke, no lactic acidosis, no typical childhood/adolescence onset</td>
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symptoms would be unexplained. Imaging along with the myriad of signs and symptoms in this case also excluded stroke, intracranial haemorrhage, multiple sclerosis, and space occupying lesions such as tumors or abscesses. Multiple sclerosis would indeed be a possible diagnosis in a female patient of this age however it was further excluded by the lack of oligoclonal bands in the cerebrospinal fluid [28]. There was no biochemical evidence of possible metabolic causes like hypoglycaemia or electrolyte imbalance. Furthermore, there was no toxin or drug use, no history of head trauma, or nutritional deficiency. Prion diseases may affect both animals and humans, the most common being CJD. They have a long incubation period but are rapidly progressive, incurable and fatal. CJD should be considered in any patient who presents with rapidly progressive neuropsychiatric symptoms. The definite diagnosis is made by brain biopsy and western blot analysis. Interestingly, a previous report described a case of EAATD presenting in a similar manner [29]. However, the case reported in our manuscript did not meet criteria outlined by World Health Organization for diagnosis of CJD. Psychiatric conditions like severe depression were also considered, however her history was not reflective of this and some clinical manifestations, namely hypothermia and bradycardia, were not consistent with a psychiatric pathology.

The mainstay of the treatment of EAATD is represented by high-dose steroids with subsequent tapering dose. EAATD usually responds to the treatment very quickly and the prognosis is generally favorable. The treatment should be prescribed for a minimum of 6 months and in most cases does not require more than 12 months [6]. However, relapse or recurrence of the symptoms, as well as resistance to the treatment with steroids may occur [3]. In these cases, other options including intravenous immunoglobulin and plasmapheresis may be prescribed [3, 6]. As a point of interest, immunosuppression has rarely been used for maintenance EAATD therapy. De Holanda and colleagues described a case of EAATD treated initially with prednisolone monotherapy, with the addition of azathioprine during the steroid-tapering process [9]. In the patient described above, alternative immunosuppression might have been considered in an effort to reduce the cumulative corticosteroid exposure, considering her history of osteoporosis and cataracts.

In conclusion, EAATD still represents a diagnostic challenge as the clinical presentation varies widely and there are no reliable diagnostic markers. In the setting of the heterogeneous clinical manifestations of EAATD, also neurovegetative/autonomic symptoms can exceptionally occur.

**Disclosure**

None of the authors have any potential conflicts of interest associated with this case report.

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**References**


