Auditory seizures in autoimmune epilepsy: a case with anti-thyroid antibodies

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ABSTRACT – In its classic presentation, Hashimoto’s encephalopathy is an acute-subacute complex neuropsychiatric syndrome with cognitive impairment, hallucinations, myoclonus, tremor or ataxia, associated with elevated anti-thyroid antibodies. Corticoids and immunotherapy are dramatically effective. However, in some cases, not all the associated features are presented and this delays diagnosis and appropriate treatment. We describe a man with abrupt onset of recurrent auditory seizures resulting in refractory non-convulsive status epilepticus. The patient was diagnosed with an autoimmune encephalopathy with elevated serum and CSF anti-thyroid antibodies. None of the antiepileptic drugs were successful, however, following immune-modulating therapy, the refractory non-convulsive status epilepticus dramatically improved, as did the patient overall. We suggest that Hashimoto’s encephalopathy should be suspected in otherwise healthy patients with unexplained new-onset focal recurrent auditory seizures which do not respond to antiepileptic drugs. The presence of anti-thyroid antibodies in the CSF supports this diagnosis.

Key words: Hashimoto’s encephalopathy, autoimmune encephalopathy, status epilepticus, anti-thyroid antibodies

Autoimmune encephalopathies frequently present with new-onset recurrent seizures, and rarely with refractory status epilepticus (r-SE). Pathogenic intracellular or surface antibodies are detected in the majority of cases, but few are of undetermined origin, such as Hashimoto’s encephalopathy (HE or steroid-responsive encephalopathy associated with autoimmune thyroiditis) (Davis and Dalmau, 2013). HE is associated with elevated anti-thyroxinperoxidase antibodies (A-TPOs) and anti-thyroglobulin antibodies (A-TAs) both in the serum and the cerebrospinal fluid (CSF). However, the diagnostic significance of the CSF assay has not yet been clarified (Ferracci et al., 2003).
thyroid antibodies. While no antiepileptic drug was immediately stopped due to a diffuse skin rash. Six days later, the patient was on LEV at 2,000 mg, LCS at 200 mg, and PHT at 600 mg daily, yet he presented with very frequent (almost 10 daily) focal seizures. Brain MRI and lumbar puncture were repeated (and were unchanged), and total-body CT and PET scans and tescal and thyroid echography were normal.

Ten days later, the patient developed a refractory non-convulsive (NC) SE presenting with a stuporous state and was moved to the Intensive Care Unit. A 24-hour treatment with midazolam and propofol had no benefit. Therefore, the patient was given thiopental (5 mg/kg/h) for three days. Concurrent EEG monitoring showed a burst-suppression pattern with intermittent epileptic discharges (figure 1E), which prevailed on the left frontal-temporal regions. MRI, performed for the third time, was unchanged. NCSE persisted after thiopental discontinuation (figure 1F) and the patient appeared with eyes open, mute, and not responding to orders.

With a suspicion of immune-mediated encephalitis, intravenous immunoglobulins (IVIG; 0.4 g/kg/day) were administered over five days, with a significant clinical improvement three days later. Methylprednisolone, 1,000 mg IV for five days, was also added, inducing a complete clinical recovery and EEG normalization within 10 days. Brain MRI hyperintensities resolved within three months. LCS and LEV were gradually tapered off, whereas PHT continued to prevent seizure relapses. The final CSF analysis showed elevated A-TA and A-TPO indices (AI), respectively (AIATA=4.00 [normal range: 0.30-1.50] and AIANTIPO=1.57 [normal range: 0.30-1.50]). Six months later, the patient was able to resume work and everyday activities, and one year later, he was relapse-free without any immunotherapy and no antiepileptic drugs.

**Discussion**

To the best of our knowledge, this is the first report of an acute onset of recurrent auditory seizures, resulting in r-SE, in a patient suffering from an autoimmune encephalopathy with elevated serum and CSF antithyroid antibodies. While no antiepileptic drug was successful, the r-SE, as well as the patient overall,
Figure 1. (A) Video-EEG showing left focal seizures with a left fronto-temporal rhythmic theta activity, while the patient described a sensation of “buzzing and ticking” on his left side. (B) Occasionally, the epileptiform activity involved the posterior and contralateral fronto-temporal region. (C) During seizures, the patient was able to recognize objects. (D) The “strong unclear noises” and the rhythmic discharges suddenly stopped. Subsequent postictal slow waves were recorded in the same regions. (E) EEG monitoring during thiopental infusion showed a burst-suppression pattern with intermittent diffuse epileptic discharges. (F) After thiopental discontinuation, continuous diffuse epileptic discharges persisted.
Figure 2. Brain MRI showed an area of T2/FLAIR hyperintensity of <8 mm in diameter in the right insula and inferior temporal gyrus without gadolinium enhancement.

dramatically improved after treatment with steroids and IVIGs.
As shown by the ictal video-EEG, left-sided auditory hallucinations were ipsilateral to the seizure discharge. It is generally assumed that unilateral auditory aura relates to the contralateral cortex. However, a study on a large cohort of patients did not confirm such a lateralizing value (Clarke et al., 2003; Florindo et al., 2006). At first, we excluded metabolic, endocrine, infectious or other anatomical causes of acute encephalopathy. The immunological hypothesis was considered later, because of the drug-resistant SE. The patient had type 1 diabetes, strongly suggesting an autoimmune susceptibility. However, an extensive panel of anti-neuronal antibodies were shown to be negative, which delayed treatment. Initially, HE was not considered because of the rather atypical presentation, including the fact that the patient was male, with no history of thyroid disease, and had normal thyroid function. Moreover, the EEG showed recurrent left fronto-temporal focal seizures without any slowing of the background activity. Initially, brain MRI was not helpful, since it did not show any lesion related to the seizure onset zone. Rather, it revealed some mild cortical abnormalities on the contralateral side that could possibly suggest an immune-mediated process, but only retrospectively. This is not surprising since imaging of HE may show non-specific white matter hyperintensities in half of the cases (Laurent et al., 2016) and be completely normal in the remainder (Castillo et al., 2006, Hilberath et al., 2014). Therefore, the diagnosis of HE relied on the unexpected evidence of intrathecal A-TA and A-TPO antibodies. A focus on CSF did not show any intrathecal IgG synthesis, however A-TA and A-TPO indices are comparatively more effective in revealing antigen-specific IgGs (Jarius et al., 2012). A-TA and A-TPO in the CSF are not routinely tested when HE is suspected, since their role has not yet been entirely clarified. However, up to 75% of HE cases, when investigated, presented with CSF antibodies, which are absent in the healthy population (Ilias et al., 2015). Autoimmune encephalopathy related to anti-thyroid antibodies is a treatable condition that can become severe, resulting in r-SE. Thus, clinicians should also consider “atypical” forms of HE without any previous thyroid dysfunction.

Conclusion
In HE patients presenting with only some of the associated features, epileptic autoimmune encephalopathy can be determined based on the presence of anti-thyroid antibodies. This condition should be suspected in cases with unexplained new-onset recurrent seizures, with focal origin and auditory manifestations which do not respond to first and second-line antiepileptic treatments. The finding of anti-thyroid antibodies in the CSF supports this diagnosis.

Disclosures.
None of the authors has any conflict of interest to disclose.

References
Atypical Hashimoto's encephalopathy


