Clinical commentary

Epileptic Disord 2017; 19 (1): 99-103

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

Claudia Varrasi [1], Domizia Vecchio [1], Luca Magistrelli [1], Gionata Strigaro [1,2], Laura Tassi [3], Roberto Cantello [1]

[1] Department of Translational Medicine, Section of Neurology, University of Piemonte Orientale, Novara
[2] CRRF Mons. L. Novarese, Neurorehabilitation Unit, Moncrivello, VC
[3] "C. Munari" Epilepsy Surgery Centre, Niguarda Hospital, Milan

Received November 18, 2016; Accepted February 2, 2017

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

Correspondence:
Gionata Strigaro
Department of Translational Medicine, Section of Neurology, University of Piemonte Orientale "A. Avogadro", Via Solaroli 17, 28100 Novara, Italy
<gionata.strigaro@med.uniupo.it>
<gionata.strigaro@gmail.com>

doi:10.1684/epd.2017.0904

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-thyroperoxidase 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).

HE prevalence is estimated to be two cases per 100.000, and predominantly affects women (Olmez *et al*., 2013). Some patients have no history of thyroid disorders and normal hormone function (Olmez *et al*., 2013). Classically, HE is a complex neuropsychiatric syndrome, including acute or sub-acute cognitive impairment, hallucinations, myoclonus, tremor or ataxia (Kirshner, 2014). Seizures occur in 60-70% of cases, and the incidence of r-SE varies from 4 to 40% of epileptic events (Monti *et al*., 2011; Tsai *et al*., 2015). On the other hand, acoustic hallucinations are encountered typically in NMDAR-antibody encephalitis and have not been reported in other forms of autoimmune epilepsy, especially HE (Gaspard *et al*., 2015).

Here, we describe a man with abrupt onset of ictal auditory manifestations, followed by r-SE, related to an autoimmune epileptic encephalopathy with antithyroid antibodies.

Case study

A 48-year-old Italian man was referred to our Neurological Department with a one-month history of recurrent episodes of unilateral left-sided auditory hallucinations. Occasionally, he also complained of associated dysgeusia and bizarre behaviour with irritability. These symptoms occurred once or twice a week, at the very onset, but daily when he was admitted to hospital. No concurrent headache or fever was described. Familial and personal medical history was unremarkable, except for type 1 diabetes mellitus since the age of 15. Neurological examination was normal, and cognitive dysfunction, anxiety or depression were excluded. Routine blood tests and metabolic, endocrine, infectious and autoimmune markers were non-remarkable, except for high blood glucose; ATAs: 218 IU/ml (normal range: 0-60); A-TPOs: 541 IU/ml (normal range: 0-60). The thyroid and TSH profile was normal.

Video-EEG monitoring allowed recording of three focal left-onset seizures, when the patient described "buzzing and ticking followed by strong unclear noises in the left ear". There was no confusion or alteration of consciousness. Seizures were stereotyped and prolonged, lasting 4 to 5 minutes. Ictal EEG showed a left fronto-temporal rhythmic theta activity, with subsequent spreading to the left and then bilateral posterior regions (*figure 1A-D*). MRI showed two FLAIR hyperintense lesions, <8 mm diameter, one in the first right short insular gyrus, the other in the basal right temporo-polar region, without gadolinium enhancement (*figure 2*). A first lumbar puncture was performed, and CSF analysis showed no cells, 37 mg/dl protein, and identical IgG bands in the serum and the CSF with a Link index of 0.4, suggesting a systemic immune reaction. The screening for neurotropic viruses was negative. No intracellular or neuronal cell surface antibodies were detected in either the serum or the CSF (against Hu, Yo, Ri, CRMP5, amphiphysin, MA2, NMDA receptor, Ampar, GABAB1R, LGI1, GAD and CASPR2).

First-line medication, such as intravenous diazepam (20 mg) and intravenous phenytoin (PHT; load: 10 mg/kg; maintenance: 400 mg/day), were ineffective. Levetiracetam (LEV) and lacosamide (LCS) were gradually started as add-on since carbamazepine (CBZ) 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 testicular 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 fronto-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 (AI_{ATA}=4.00 [normal range: 0.30-1.50] and $AI_{antiTPO}$=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,

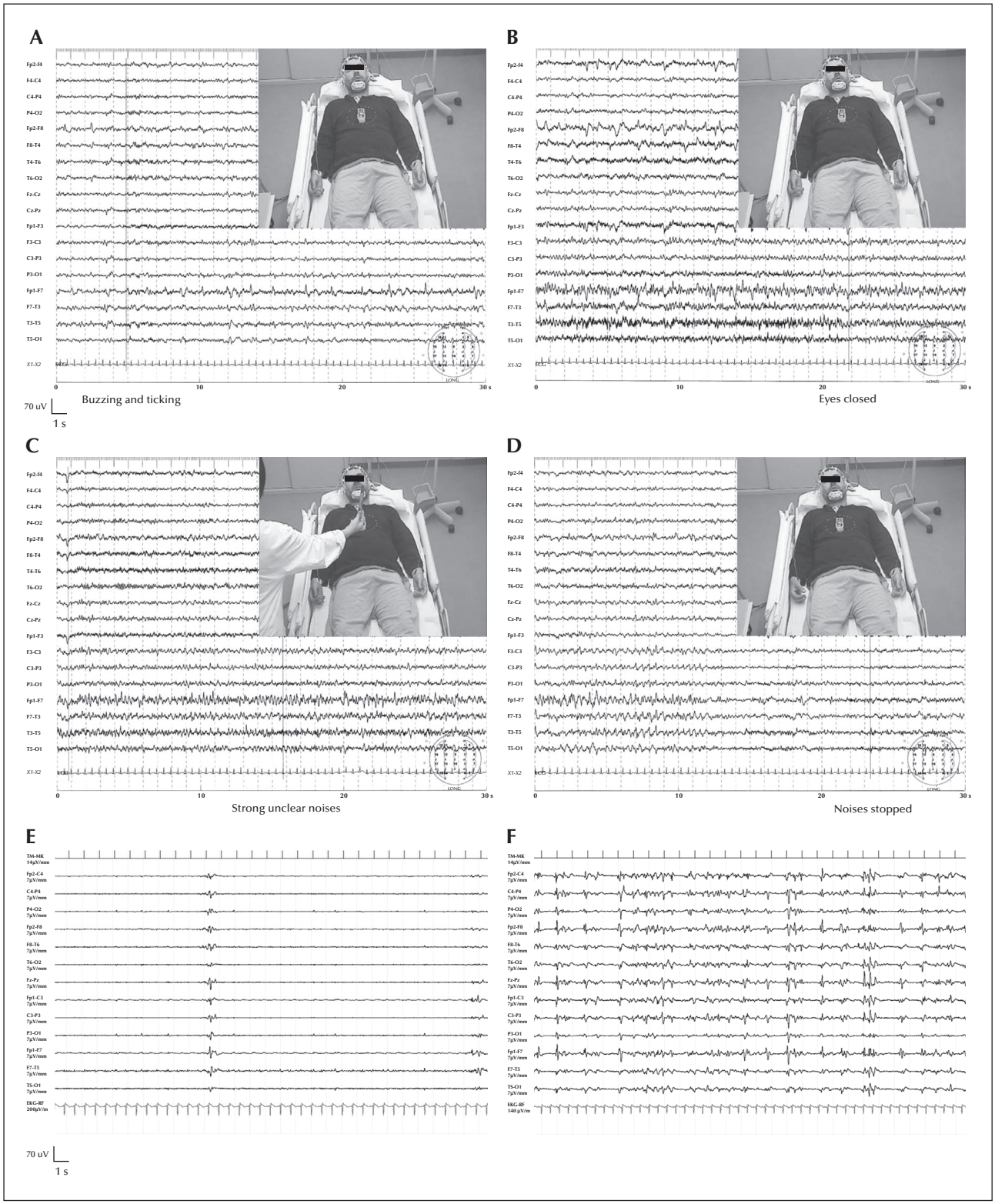

Figure 1. (A) Video-EEG showing left focal seizures with a left fronto-temporal rhythmic theta activity, while the patient described a sensation of "buzzing and ticking" on his left side. (B) Occasionally, the epileptiform activity involved the posterior and contralateral fronto-temporal region. (C). 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.

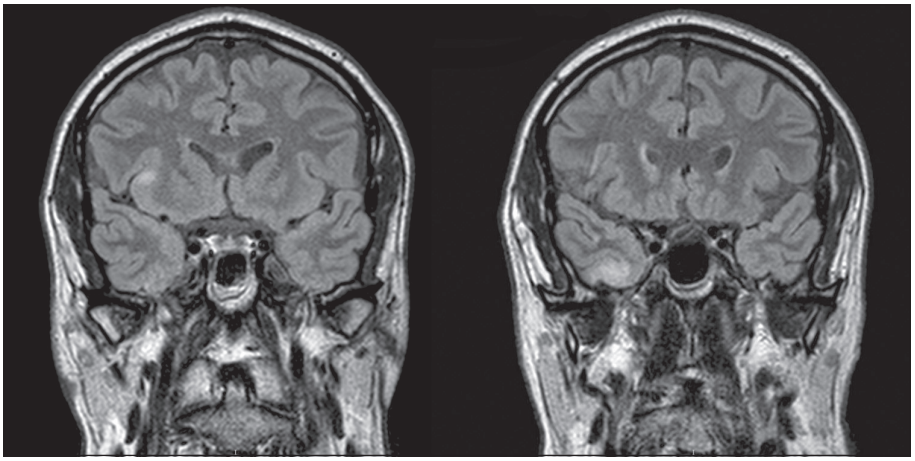

Figure 2. Brain MRI showed an area of T2/ FLAIR hyperintensity of <8 mm in diameter in the right insula and inferior temporal gyrus without gadolinium enhancement.

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

Castillo P, Woodruff B, Caselli R, *et al*. Steroid-responsive encephalopathy associated with autoimmune thyroiditis. *Arch Neurol* 2006; 63: 197-202.

Clarke DF, Otsubo H, Weiss SK, *et al*. The significance of ear plugging in localization-related epilepsy. *Epilepsia* 2003; 44: 1562-7.

Davis R, Dalmau J. Autoimmunity, seizures, and status epilepticus. *Epilepsia* 2013; 54(6): 46-9.

Ferracci F, Moretto G, Candeago RM, *et al*. Antithyroid antibodies in the CSF: their role in the pathogenesis of Hashimoto's encephalopathy. *Neurology* 2003; 60: 712-4.

Florindo I, Bisulli F, Pittau F, *et al*. Lateralizing value of the auditory aura in partial seizures. *Epilepsia* 2006; 47(5): 68-72.

Gaspard N, Foreman BP, Alvarez V, *et al*. New-onset refractory status epilepticus: etiology, clinical features, and outcome. *Neurology* 2015; 85: 1604-13.

Hilberath JM, Schmidt H, Wolf GK. Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT): case report of reversible coma and status epilepticus in an adolescent patient and review of the literature. *Eur J Pediatr* 2014; 173: 1263-73.

Ilias I, Karagiorga V, Paraskevas G, *et al*. Thyroid autoantibodies in the cerebrospinal fluid of subjects with and without thyroid disease: implications for Hashimoto's encephalopathy. *J Thyroid Res* 2015; 2015: 819072.

Jarius S, Eichhorn P, Wildemann B, Wick M. Usefulness of antibody index assessment in cerebrospinal fluid from patients negative for total-IgG oligoclonal bands. *Fluids Barriers CNS* 2012; 9: 14.

Kirshner HS. Hashimoto's encephalopathy: a brief review. *Curr Neurol Neurosci Rep* 2014; 14: 476.

Laurent C, Capron J, Quillerou B, *et al*. Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT): characteristics, treatment and outcome in 251 cases from the literature. *Autoimmun Rev* 2016; 15: 1129-33.

Monti G, Pugnaghi M, Ariatti A, *et al*. Non-convulsive status epilepticus of frontal origin as the first manifestation of Hashimoto's encephalopathy. *Epileptic Disord* 2011; 13: 253-8.

Olmez I, Moses H, Sriram S, Kirshner H, Lagrange AH, Pawate S. Diagnostic and therapeutic aspects of Hashimoto's encephalopathy. *J Neurol Sci* 2013; 331: 67-71.

Tsai MH, Fu TY, Chen NC, *et al*. Antithyroid antibodies are implicated in epileptogenesis of adult patients with epilepsy. *Medicine (Baltimore)* 2015; 94: e1059.