Case Report

Recurrent status epilepticus associated with Hashimoto's encephalopathy

H. Visée a,*, C. Mabiglia b, V. Vanderaespoldien c, M.-D. Gazagnes a, G. Glibert a

a Department of Neurology, Brugmann University Hospital, Brussels, Belgium
b Department of Radiology, Brugmann University Hospital, Brussels, Belgium
c Department of Neuro-psychology, Brugmann University Hospital, Brussels, Belgium

A B S T R A C T

Hashimoto's encephalopathy (HE) is an infrequent disease with no well-known physiopathology. Status epilepticus is rarely reported in association with HE. We describe the 7-year evolution of a young woman who presented with recurrent status epilepticus as the main complication of HE. This evolution was especially marked by the occurrence of steroid-refractory symptoms and a poor outcome with persistent cognitive and behavioral consequences. We point out that the frontal lobes are especially implicated in these symptoms. This patient highlights the risk of multiple relapses and the need for a long follow-up period. We describe her clinical and paraclinical features, compare this patient to similar case reports, and comment on her outcome.

1. Introduction

"Hashimoto's encephalopathy" (HE), also called "steroid-responsive encephalopathy associated with autoimmune thyroiditis" (SREAT), is a rare condition that associates an encephalopathic state with an autoimmune-mediated lymphocytic infiltration of the thyroid gland (Hashimoto's thyroiditis, HT). The physiopathology of HE remains unknown. A humoral autoimmune process is supported by the finding of antineuronal [1] or anti-α-enolase antibodies [2]. Other anti-CNS autoantibodies could be involved in the occurrence of HE, which might explain the variability of the clinical features [1]. A vasculitic process is not excluded in some patients, supported by stroke-like symptoms and necrotic sequelae observed on brain MRI [3]. Although it is not certain whether they have a true physiopathologic meaning, the high titer of antithyroid antibodies leads to the diagnosis of HE, after exclusion of other causes of encephalopathy. The prevalence of HE is estimated at 2.1/100,000 [4]. Since a large panel of unspecific neuropsychiatric symptoms can manifest during HE and before disclosing HT, its prevalence is probably underestimated. Cognitive symptoms (as confusion, memory loss, attention deficit, ...), psychiatric symptoms (as hallucinations, psychosis, anxiety, agitation, jitteriness, ...), alteration of consciousness, seizure, tremor, ataxia, and stroke-like episodes can all be the first signs of the disease. Two clinical pictures were described by Kothbauer-Margreiter et al., a diffuse progressive type and a vasculitic type with stroke-like episodes [5]. Seizures are reported in both and more frequently in the diffuse type. Other authors reported seizures in 66% of HE, including status epilepticus (SE) in 12% [6]. Focal, generalized, myoclonic seizures and SE are described in association with HE. As discussed by Ferlazzo et al., SE is generally resistant to antiepileptic drugs (AEDs) and needs steroids to improve [7]. To evaluate the outcome of HE, only short series are reported. In a series of 20 patients with HE [5], steroid responsiveness is excellent in 90%, relapses following steroid dose reduction occur in 40%, immunosuppressive drugs (ISDs) are used in 10%, persistent cognitive symptoms remain in 15%, and uncontrolled relapses persist in 10%. Concerning the issue of SE as a complication of HE, only a few cases are reported in the literature with often a short follow-up period, rendering their late outcome not well known.

2. Case report

In 2006, a 26-year-old woman without relevant medical story developed tremor, confusion, agitation, and blurred vision during a few weeks. A first episode of refractory generalized convulsive status epilepticus (GCSE) followed and required anesthetic agents to improve. A prolonged postictal status with bradyphoria, ataxia, and tremor followed. The EEG was diffusely slowed. A slight right periventricular T2/FLAIR hyperintensity was observed on brain MRI. No toxic, metabolic, or infectious etiologies were identified. She recovered but promptly had a second episode of refractory GCSE despite...
oral phenytoin and required anesthetic agents again. The postictal period was prolonged anew with encephalopathy status. The EEG was diffusely slowed with occasional right frontal rhythmic theta period, and a focal right paramedian frontal hyperperfusion. A mild elevation of protein content without oligoclonal bands was found in the cerebrospinal fluid. The autoimmune screening in the serum disclosed high titers of antithyroglobulin (274 IU/mL, normal <60 IU/mL) and antithyroperoxidase (602.8 IU/mL, normal <60 IU/mL) antibodies, with euthyroid status. Thyroid ultrasound was compatible with thyroiditis status. Full body PET scan and CT scan did not reveal neoplastic disease. Onconeural antibodies (anti-HU, anti-Yo, and anti-Ri) were negative. The diagnosis of HE was probable. The EEG normalized rapidly after intravenous methylprednisolone (1 g/day), and the patient recovered. Phenytoin was discontinued. At this stage, her cognitive functions were almost normal with small deficits for free recall (episodic memory), selective attention, and verbal fluency (Table 1).

Ten months later, steroids were progressively reduced because of side effects (osteoporosis, Cushing-like syndrome, diabetes). A generalized convulsive seizure relapsed rapidly. Phenytoin and steroids were discontinued after six courses of cyclophosphamide. For 3 years, she was free of treatment and seizures. Postural tremor, nervousness, and anxiety persisted. In 2010, she presented a short collapse without loss of consciousness relapse under 8 mg of oral methylprednisolone. In 2013, she continues to use chronically antiepileptic drugs (levetiracetam, phenytoin, and phenobarbital) and low dose of oral methylprednisolone.

### 3. Discussion and conclusion

We report the 7-year follow-up of a young woman who presented with recurrent status epilepticus associated with Hashimoto’s encephalopathy. This diagnosis is sustained by high titer of antithyroid antibodies and the exclusion of other toxic, metabolic, infectious, or paraneoplastic etiologies. Through lack of typical features of limbic encephalitis or N-methyl-D-aspartate receptor antibody (NMDAR-Ab) encephalitis, a complete screening of antibodies (Ab) against neuronal surface antigens (as voltage gate potassium channel (VGKC) complex Ab, glutamic acid decarboxylase (GAD) Ab, α-amino-3-hydroxy-5-methyl-4-isoxasolepropionic acid receptor (AMPA) Ab, and gamma-aminobutyric acid B receptor (GABABr) Ab) has not been performed.

Only a few cases of status epilepticus associated with HE have been reported, and some are shown in Table 2. Including our cases, all present the clinical diffuse progressive type of HE proposed by Kothbauer-Margreiter et al. with first symptoms equally distributed between thyroid dysfunction, behavioral changes, or SE. This distribution emphasizes the clinical variability and the necessity to look for antithyroid Ab in the case of SE of unknown origin.

Her evolution was first characterized by a frontal EEG and SPECT focalization in the course of a GCSE episode. Later, while spike–wave discharges showed a diffuse spreading leading to an especially prolonged NCSE, diffuse mesiotemporal and frontal postictal edema was observed on the brain MRI. Seizures of frontal origin [14] or temporal origin [15,16] have both been reported to be associated with HE. Among the patients listed in Table 2 and using different diagnostic procedures (brain MRI, PET scan, SPECT, or EEG), frontal dysfunction is more frequently observed (6/10) than mesiotemporal dysfunction (1/10).

From a therapeutic point of view, her evolution was marked by successive steroid responsiveness, steroid dependence, prolonged remission after cyclophosphamide courses, late relapse of steroid-resistant symptoms, and thereafter persisting steroid dependence. No correlation could be made between the occurrence of steroid-resistant symptoms and a delay in the beginning of intravenous methylprednisolone. Steroid-resistant SE as a complication of HE seems to be infrequent (2/11, including our patient and one patient

### Table 1

Summary of neuropsychological test results.

|                      | March 2007 | September 2011 | April 2012 |
|----------------------|------------|----------------|------------|
| MOCA, global score [8]| 10/10      | 1/10           | 3/10       |
| Episodic memory      |            |                |            |
| – Free recall         | 42/64 [9]  | 0/4* [10]      | 0/4* [10]  |
| – Cued recall         | 63/64 [9]  | 0/4* [10]      | 0/4* [10]  |
| – Recognition         | 16/16 [9]  | 0/4* [10]      | 3/4 [10]   |
| Short-term memory     |            |                |            |
| – Digit span forward  | 4*         | 4*             | 3*         |
| – Digit span backward |           |                | 4          |
| Executive functions   |            |                |            |
| – Trail Making Test A [11]| 24 s  | 1/1 [8]        | 8/18*      | 4/15th     |
| – Trail Making Test B [11]| 48 s  |                | 5* [8]     | 8*         |
| – Frontal Assessment Battery [12] | | 21 |            |
| – Phonological verbal fluency | 19 |                |            |
| – Semantic verbal fluency | 21  |                |            |
| Visual attention test |            |                |            |
| – Bell Cancelation Test [13] | 5 omissions, 0 false detections, 125 s | Impaired | 2 omissions, 16 false detections, 375 s |
| Visuospatial abilities |            |                |            |
| – Clock Drawing Test [8] | 3/3     | 0/3*           | 2/3        |

* Pathological results with ≥2 standard deviation under the average.

* Incomplete test.
in Table 2) but does not exclude the diagnosis. As reported by other authors [5], a correlation has not been observed between relapses and the level of antithyroid-Ab (Fig. 3), sustaining the hypothesis that they do not play a part in the physiopathological development of HE.

The outcome of most patients (8/11) listed in Table 2 is favorable but has been commonly observed in a short follow-up period and often with ongoing steroid or ISD use, making the conclusions debatable. Early (2/11) and late (2/11) relapses following suspension of steroid or ISD use are reported. One death occurred in the course of a steroid-resistant SE. Two (including our patient) remain cognitively deficient as sequelae of prolonged steroid-resistant SE.

In conclusion, this case report emphasizes the possible frequent relapses of SE as a complication of HE and the possible evolution towards steroid-resistant SE. Clinicians should be aware that relapses can occur early or even late after tapering of steroid or ISD use; therefore, a long follow-up period should be advisable. Moreover, since the antithyroid antibodies could not been used as markers of encephalopathy’s relapses, the question of the continuation of the immunomodulatory of immunosuppressive drugs remains an open debate.

References

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Fig. 1. T2 and FLAIR images show hyperintense lesions in bilateral frontal lobes and thalamic and mesiotemporal regions (better seen on coronal FLAIR images). T1-weighted images show no contrast enhancement after gadolinium injection.
Fig. 2. (A) Interictal EEG characterized by diffuse slowing and frontal spike-waves. (B) Ictal EEG characterized by subtle SE of frontal origin.
Table 2

| Ref | Age, sex | Type of seizure | 1st signs | Brain MRI, SPECT/PET scan | EEG | Control SE with | Follow-up |
|-----|----------|-----------------|-----------|---------------------------|-----|----------------|-----------|
| [17]| 36, f   | CPSE CPSE       | MRI: left posterior frontal hypersignal | MRI: normal | Slow | uk | uk | Remission at 2 W |
| [18]| 61, f   | NCSE HD         | MRI: normal | MRI: left posterior frontal hypersignal | MRI: normal | Generalized sharp and slow waves discharges | S | |
| [19]| 79, f   | Focal seizure BC | MRI: generalized atrophy, leukoaraiosis | MRI: normal | Diffuse or multifocal slowing | AEDs | Relapsed encephalopathy few M after S, 4 M after ISDs, remission at 6 M with ISDs and S |
| [20]| 37, f   | Multifocal motor SE GTCS | 1st MRI: normal | 2nd MRI: hypersignal in both precentral and left postcentral gyrus MRI: normal | Diffuse slowing, asynchronous left or right central sharp waves | S | Remission at 15 M with AEDs and ISDs |
| [21]| 27, f   | GTCS GCSE HD    | MRI: normal | SPECT: frontal hypoperfusion | MRI: normal | Diffuse slowing, bifrontal theta activity, photomyoclonia | AEDs | Relapsed AEDs and S-resistant SE; death |
| [7] | 41, m   | GCSE GCSE       | MRI: normal | SPECT: frontal hypoperfusion | MRI: normal | Lctal: generalized epileptic activity Postictal: slow, intermittent frontotemporal bilateral slowing | S | Remission at 1 Y with S, AEDs and HS |
| [9] | 16, f   | GCS, CPSE BC    | MRI: right mediotemporal hypersignal Ictal SPECT: right parietotemporal hyperperfusion | MRI: right mediotemporal hypersignal Ictal SPECT: right parietotemporal hyperperfusion | Ictal EEG: rhythmic delta waves on the right hemisphere | S | Remission at 2 M |
| [22]| 63, f   | GTCS, NCSE BD   | MRI: lacunar infarct | Pet scan: right frontal hypometabolism | MRI: normal | Bilateral frontotemporal continuous epileptic activity | AEDs | Executive function impairment at 3 Y |
| [8] | 51, f   | NCSE HD         | MRI: normal | MRI: normal | Bifrontal and generalized slow waves | S | Relapsed NCSE at 2 Y; Remission at 3 Y, with AEDs |
| [8] | 66, f   | NCSE NCSE       | MRI: normal | MRI: normal | Bifrontal and generalized slow waves | S | |

AEDs, antiepileptic drugs; BC, behavioral changes; BD, Basedow’s disease; CPSE, complex partial status epilepticus; GCS, generalized convulsive seizure; GCSE, generalized convulsive status epilepticus; GTCS, generalized tonic–clonic seizure; HD, Hashimoto’s disease; HS, hormonal substitution; ISDs, immunosuppressive drugs; M, months; NCSE, nonconvulsive status epilepticus; S, steroids; SE, status epilepticus; uk, unknown; W, weeks; Y, years.

Fig. 3. Line graph showing no correlation between antithyroglobulin (anti-TG) or anti-thyroperoxidase (anti-TPO) antibodies and events as status epilepticus (SE) or generalized convulsive seizure (GCS).