Cortico-responsive encephalopathy associated with autoimmune thyroiditis (SREAT): about two case reports characterized by a gap between the diagnosis of autoimmune thyroiditis and neurological disorders

Original article

Encéphalite sensible aux corticoïdes : tableau neurologique des années à distance de la mise en évidence d’une auto-immunité antithyroïdienne.
À propos de deux observations et brève revue de la littérature

J. Lopez-Giovaneli, O. Moreaud, P. Faure, I. Debaty, O. Chabre, S. Halimi*

*Département Diabète Urologie Néphrologie Endocrinologie (DUNE), CHU de Grenoble, BP 217, 38043 Grenoble cedex 9, France

Département de neurologie, CHU de Grenoble, BP 217, 38043 Grenoble cedex 9, France

Département de biologie intégrée, CHU de Grenoble, BP 217, 38043 Grenoble cedex 9, France

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Résumé

Nous rapportons deux observations d’encéphalopathies de Hashimoto qui offrent la particularité rare, que dix à 20 années ont séparé les manifestations neurologiques et la mise en évidence d’une auto-immunité antithyroïdienne. Très peu d’observations similaires ont été rapportées jusqu’alors. Un tel délai ne peut qu’accentuer la difficulté de retenir cette cause d’encéphalopathie déjà volontiers ignorée. Ici, comme cela signe cette entité, la corticothérapie a fait disparaître de manière spectaculaire l’ensemble des symptômes. Nos deux patients n’ont présenté aucune rechute trois ans après l’arrêt de tout traitement. Nous suggérons de rechercher la présence d’anticorps antithyroïdiens devant tout tableau neuropsychiatrique inexpliqué, aigu ou subaigu et de présentation très polymorphe. Chez des sujets âgés cette cause de démence ne doit pas être exclue tant le traitement peut être aisé, quoique dans ce contexte la maladie de Creutzfeldt-Jacob et surtout la maladie d’Alzheimer soient plus plausibles. Une brève revue synthétique de la littérature est effectuée.

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Abstract

We report two cases of steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT) often called “Hashimoto’s encephalopathy” in which the neurological manifestations develop years before or after the Hashimoto’s diagnosis. Because of this specific presentation, the etiological diagnosis of this type of encephalopathy can be a difficult task. In our patients there was a gap of 10 to 20 years between the proof of autoimmune thyroiditis and the neurological symptoms. Case reports of this type of presentation are rare in the literature. A dramatic responsiveness to steroids with total recovery, after several relapses, was confirmed 3 years after the end of treatment. We suggest that antithyroid antibodies should be checked in all patients with unexplained acute or subacute encephalopathy even in elderly subjects in whom the most important differential diagnosis with Creutzfeldt-Jacob disease remains rapidly progressive Alzheimer’s disease. A brief review of the literature is proposed.

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Mots clés : Encéphalite sensible au corticostéroïdes ; Anticorps antithyroïdiens ; Démence, Corticothérapie

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1. Introduction

Hashimoto’s encephalitis, a term which defines a poorly understood entity, is supposed to be a relatively rare condition, often misdiagnosed. It is observed in a small percentage of patients presenting with autoimmune thyroid disease, high levels of antithyroid antibodies, associated with various neurological and psychiatric disorders [1–4]. Clinical symptoms are often associated with high CSF protein levels, diffuse abnormal electroencephalography (EEG) and variable magnetic resonance imaging (MRI) findings. However, this disease is never based on strict evidence. The responsiveness to steroids with total recovery, sometimes after several relapses, strongly suggests the diagnosis of Hashimoto’s encephalopathy. Thus this syndrome is also defined as “corticosteroid-responsive encephalopathy” associated with autoimmune thyroiditis. Although the pathogenic sequence of this encephalopathy is better characterized, some authors consider that this entity reflects an understood entity, is supposed to be a relatively rare condition, often misdiagnosed. It is observed in a small percentage of patients presenting with autoimmune thyroid disease, high levels of antithyroid antibodies, associated with various neurological and psychiatric disorders [1–4]. Clinical symptoms are often associated with high CSF protein levels, diffuse abnormal electroencephalography (EEG) and variable magnetic resonance imaging (MRI) findings. However, this disease is never based on strict evidence. The responsiveness to steroids with total recovery, sometimes after several relapses, strongly suggests the diagnosis of Hashimoto’s encephalopathy. Thus this syndrome is also defined as “corticosteroid-responsive encephalopathy” associated with autoimmune thyroiditis. Although the pathogenic sequence of this encephalopathy is better characterized, some authors consider that this entity reflects an association rather than causation [1]. Nevertheless, it is particularly important to early diagnose this condition since one of its fundamental characteristics is the excellent response to high doses of steroids. Few cases show that clinical manifestations of SREAT can anticipate by years the diagnosis of Hashimoto’s thyroiditis [5]. We report two cases of SREAT on four consecutive patients, in which the first neurological manifestations appeared years before or after the Hashimoto’s diagnosis.

2. Case reports

2.1. Case 1

In July 2003, a 60-year old woman, while she was hospitalized for investigating multiple articular pains, suddenly exhibited visual disorder as dyschromatopsy, variable along the day, and nocturnal hallucinations described as nightmares. The day after, occipital and cervical headaches appeared, associated with urinary incontinence and vomiting. She was referred to our neurology department, where sudden blindness and confusion with psychomotor agitation were added to the initial presentation.

The patient had a 20-year old history of elusive and self-regressive headache and vertigo episodes, which led in two opportunities to hospitalization. At those times, the neurological examination showed a peripheral vertiginous syndrome, but CT scan, CSF and audiometry were considered as normal and she left hospital with the diagnosis of migraine.

Her medical history included obesity, active cigarette smoking, a 10-year duration type 2 diabetes treated by oral antidiabetic drugs, a coronary heart disease but no cerebrovascular disturbances (clinical and Doppler investigations). She was receiving statin for a dyslipidemic disorder and her blood pressure was controlled by a single drug therapy. A Hashimoto’s thyroiditis has been diagnosed 10 years before and treated with L-thyroxine 100 μg/day. Clinical examination showed an unsteady gait with a wide based stance without Romberg sign. The syndrome was in favor of a static cerebellar syndrome. Cranial nerve examination was normal, except for a bilateral, sudden and transient blindness with normal photomotor reflex, a lack of blinking before the threat, all signs interpreted as cortical blindness. Mental status exam was normal except for the presence of recent memory and writing troubles. Routine biological tests were normal except for fasting blood glucose, 180 mg/dl, HbA1c 10% (N < 6%), showing a poor glycemic control, a moderately disturbed hepatic enzyme profile attributed to a liver steatosis. CRP, carcioembryonic antigen (CEA), folate and B12 vitamin blood levels were normal. An immunologic panel including latex, anti-smooth muscle, antimitochondrial, anti-parietal wall cells, antigliadin and paraneoplastic anti-Hu, anti-Yo and anti-Ri antibodies were negative as well as all serological panel, HIV, HCV, HBV, VZV, VDRL, Rickettsia, Brucella, Yersinia and Lyme diseases.

Thyroid function tests revealed a TSH of 6.6 μIU/ml (N: 0.27 – 4.2), fT3 of 3.4 pmol/l (N: 2.5 – 5.) and a fT4 of 11.9 pmol/l (N: 11.5 – 23). The anti-thyroglobulin (ATg) and antithyroid peroxidase (TPO) antibodies were significantly positive: 375 U/ml (N < 100) and 4080 U/ml (N < 60), respectively.

CSF showed a moderately high level of proteins of 81 mg/dl (N: 24 – 44) without pleocytosis and IgG level of 73 ng/l (N: 10 – 50) with a normal electrophoretic profile.

The electroencephalogram (EEG) was abnormal, showing marked slowing of basal encephalic activity, mainly on posterior regions, important amplitude attenuation and slow bilateral waves. Visual evoked potentials (VEP), showed a disturbed amplitude with undetectable response to little, big and red dimmers, but symmetric response to flashes. The cerebral MRI imaging revealed an anterior occipital subcortical white matter hyperintensity on T2, in favor of a leukencephalopathy.

The diagnosis of SREAT was evoked, and a high dose corticosteroid therapy was started, with prednisolone 60 mg/day followed by a progressive decrease of the dose.

A dramatic clinical improvement was observed, with a complete regression of visual disorders and cerebellar syndrome and a significant decline of the headaches. Paralleling with the clinical improvement, a fall of antiTPO antibodies levels to 900 μU/ml and a normalization of the MRI’s images were observed. The patient left the hospital with prednisolone 20 mg/day followed by a slow and progressive lowering of the doses.

Six months latter, she was again hospitalized because of a clinical relapse following a recent decrease of the corticosteroids dose (prednisone 10 mg/day), characterized by headaches, vertigo and visual disturbances (kaleidoscopic vision). At that time, neurological examination was strictly normal, and these symptoms quickly reversed after an adjustment of steroid doses.

Ten months latter, corticosteroid treatment has been removed and a complete neuropsychological exam showed the absence of any neurological symptoms. Three years later, her situation remained stable and the patient did not exhibit any relapse.
2.2. Case 2

A 38-year old man was also admitted in our neurology department on October 2003, because of a short period of allodynia involving both legs. The patient was an active cigarette smoker. Fifteen years before, he had presented an episode of Legionellosis (1990).

In 1993 he presented a short duration transient visual impairment. From 1998, the patient had annual and self-resolutive episodes of dysesthesias of both legs, lasting within two and three weeks, leading, one time, to a short hospitalization during which a cerebral scan was done and considered as normal. Clinical examination showed a mild spastic gait and dysesthesias of both legs, described as “pressure sensation” or “tense skin”. Routine biological tests were normal, as well as thyroid function tests. Both immunological and serological panels were negative.

CSF proteins (34 g/l, N 24 – 44), white cell count, IgG values and electrophoretic profile were all normal. An encephalic MRI did not show any abnormality. However, a medullar MRI evidenced two central-medullar hyperintensity signals on T2 sequences, one on C4 and the other on T4, both without Gadolinium enhancement, in favor of myelitis or vascular involvement.

The patient received a flash of corticosteroids (1 mg/kg/day of methylprednisolone) during 3 days, achieving a total decline of symptoms within 1 – 2 months.

Two years later (August 2005), the patient was again hospitalized because of a similar clinical feature, dysesthesias involving this time legs, lower abdomen and fingers of both hands, now described as “burning”. Clinical examination showed a mild sensitive ataxia and dysesthesias of these territories associated with impaired epiceritic sensitivity. Routine biological tests were normal, and immunological and serological panels were again negative. However, a mild increase of TSH (5.3 mU/ml, N 0.27 – 4.2) led to a dosage of antithyroid antibodies that revealed marked positive levels for antiTPO antibodies 2450 mU/l (N < 60) and anti Tg antibody 318 mU/l (N < 60). Encephalic MRI showed this time a lateral periventricular hyperintensity signal on T2 sequences not enhanced by gadolinium. Medullar MRI imaging showed two new hyperintensive signals on T2 sequences, one on C2-C3 level and the other on T1-T2 level, only the first one enhanced by gadolinium. Lesions evidenced on 2003’s medullar MRI had disappeared. A corticosteroid flash of 1 mg/kg per day of methylprednisolone was administered for 3 days with again a complete regression of symptoms after 1 – 2 months. Since then, a periodic evaluation was performed; the patient remained completely asymptomatic and thyroid function remains normal in spite of persistent highly positive antithyroid antibodies.

3. Discussion

Brain et al. firstly described Hashimoto encephalitis (SREAT) in 1966. Since that initial description, about 100 cases have been published [6].

To date pathogenesis of this encephalopathy is still unclear and largely debated, because of extremely diverse clinical presentation, possibly attributable to different aetiologic and pathophysiologic mechanisms [1,7–9]. An autoimmune mechanism has been suspected because of its high prevalence in females, fluctuating course, association with autoimmune disorders and dramatic recovery following corticosteroid therapy. The pathogenesis could involve deposition of immune complexes, reversible leukenoencephalopathy with surrounding oedema, or the presence of a shared antigen in both the thyroid gland and the brain [6–10]. An excessive, central release of TRH was held responsible for the seizures. Improvement could be obtained only with a thyroxin treatment in hypothyroidism, which supports the hypothesis of a pathogenetic role of TRH [8]. Various other hypothesis have been proposed. Both vasculitis and autoimmunity directed against common brain-thyroid antigens represent the most probable aetiologic pathways. Among other causative hypothesis, cerebral hypoperfusion, recurrent demyelinating encephalomyelitis and mitochondrial dysfunction as a result of thyroid-related antibody interference are mentioned. However, none of them have been confirmed, mainly because the fine needle biopsies are usually lacking [11–15].

SREAT generally starts in middle age with a female/male ratio 3.6/1; some cases have been reported in very young patients [16,17]. Two different clinical presentations are proposed. First, acute or subacute forms, “vasculitis like”, with stroke-like episodes, mild cognitive impairments. A second form, slow and progressive, with a psychiatric presentation, which could lead to dementia. Seizures, myoclonus, tremor and coma may occur in either form; neither presentation is exclusive and significant overlap is possible. Medullary involvement has been described.

High level of antithyroid antibodies are necessary for the diagnosis of SREAT, but thyroid function status may vary. Hypothyroidism is the most frequent presentation [18], some patients have normal thyroid function and a few patients exhibit thyrotoxicosis (Graves disease).

The CSF often shows a high protein level and a monoclonal IgG increase sometimes, observed usually without pleocytosis [2]. The EEG reveals in up to 95% of cases a slowing of basal encephalic activity [19], and MRI shows variable images, which vary from global cerebral atrophy, to normal or white-matter subcortical changes, seen as T2 hyperintensities which represent swelling or inflammation [20,21].

If SREAT is diagnosed, which can be done after eliminating vascular, infectious, tumoral, metabolic and toxic causes of encephalopathy, especially Creutzfeldt-Jacob disease (CJD), immunosuppressive therapy with high doses of corticosteroids leads to a prompt resolution of symptoms, improvement within a few days, complete in almost all cases. The dramatic improvement of clinical symptoms and normalization of EEG following corticosteroid further ruled out the possibility of CJD [22].

However, there are no specific clinical diagnosis, laboratory or neuroimaging findings. Moreover, cerebral complications may occur long before Hashimoto’s thyroiditis [23]. These
two last characteristics make the SREAT rarely suspected, delaying the diagnosis and the proper treatment, increasing the possibility of irreversible features as dementia, coma or even death.

One of our cases was a diabetic patient with macrovascular complications, but without cerebral vascular disease. Both patients presented neurological manifestations years before the autoimmune thyroiditis’s diagnosis. Fortunately, a high dose corticosteroid treatment allowed for a dramatic improvement of the neurological symptoms in both patients initially and during the relapses. Complete long term recovery was maintained in both cases (>3 years).

Both of our patients had presented a “vasculitis form” of SREAT, characterized by intermittent episodes of relapse and remission of headaches, vertigo, cerebellar syndrome and visual disturbances probably along the last 20 years in one case, and dysesthesias of both legs for 8 years in the other case. Only the first case had high CSF protein’s level. Both cases associate high antithyroid antibodies levels, cerebral and medullary MRI’s changes and a remarkable recovery after corticosteroids. These two cases, above all, illustrate the complications, but without cerebral vascular disease. Both cases associate high antithyroid antibodies levels, cerebral vasculitis, some authors have doubts regarding this entity and propose to regard antithyroid antibodies only as markers of diffuse autoimmune. Meanwhile, others consider that this disorder is relatively frequent and probably under diagnosed mainly in cohorts of subjects diagnosed as Creutzfeldt-Jacob, in the absence of 14–3–3 protein [24] or other dementias. However in elderly people, the most important differential diagnosis to Creutzfeldt-Jacob disease remains rapidly progressive Alzheimer’s disease. In younger subjects, however, chronic encephalitis, and as subgroup SREAT (Hashimoto’s encephalitis), is the most frequent disease, which has to be excluded in suspected Creutzfeldt-Jacob cases [22].

4. Conclusion

SREAT is probably a frequent cause of acute neurological disorders and encephalopathy. We suggest that antithyroid antibody levels should be checked in any unexplained acute or subacute encephalopathy. This must be done after ruling out the other major causes, especially when a relapsing course, stroke-like exacerbation, seizures, tremor or elevation of the CSF protein are found, a way to avoid the uncommon, but potentially fatal consequences of SREAT’s misdiagnosis [25].

References