Steroid responsive encephalopathy associated with autoimmune thyroiditis presenting with late onset depression

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ABSTRACT

يعتبر الاعتلال الدماغي المصاحب لالتهاب الغدة الدرقية الناجم عن المناعة الذاتية (SREAT) مرض نادر، و الذي يعرف أيضاً باعتلال الدماغ هيشماتو، و يستجيب لعلاج الكورتيزون (الستيرويد)، حيث تظهر أعراضه إما لمرة واحدة أو عدة مرات، و تشتمل هذه الأعراض على هيئة اختلاط عقلي، تشنجات، ذهان، خرف، أو أعراض مشابه للجلطات الدماغية. في هذا التقرير، نستعرض حالة أصيبت بهذا المرض حيث كان أول أعراض هذا المرض اكتئاب في مرحلة متأخرة في المرضى المتوسطي العمر، الأمر الذي يدعو إلى الاشتباه بهذا المرض كسبب للاكتئاب في عمر مجموعة المرضى هذه.

Steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT), (also known as Hashimoto's encephalopathy) is a rare autoimmune encephalitis associated with high antithyroid antibodies, and presents with a relapsing-remitting or monophasic course, consisting of confusion, seizures, psychosis, dementia, or stroke-like episodes. In this report, a late onset depression was the initial presentation of SREAT in a middle aged patient, something rarely described before, indicating the need to suspect SREAT as a possible etiology for depression in this age group.

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The early description of cases of steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT), also known as Hashimoto's encephalopathy (HE), was documented by Lord Brain in 1966,[1] and since then the interest in these cases continued despite the rarity of this disease. One of the reasons for the interest in this disease is the dramatic response to immune therapy, particularly corticosteroids, and some authors recommend a trial of steroid therapy for cases of unexplained encephalopathy with high titers of thyroid antibodies, and the non-responders to steroids were found to have atypical clinical features, and often were diagnosed to have neurodegenerative diseases.[2] Among the heterogeneous neurological and psychiatric symptoms patients with SREAT may present with, depression is a known feature.[3,4] In this report, a late onset depression in a middle aged patient was the initial presentation of SREAT, indicating the need to consider SREAT as a cause of depression in this age group, something rarely described in previous literature.[5]

Case Report. A 61-year-old right-handed lady, with unremarkable medical history, started to have sleep disturbance, loss of appetite, and loss of interest in her usual hobbies and activities, with no prior history of depression. She was evaluated by a psychiatrist, and was started on citalopram 20 mg once daily. With no clinical improvement noted after 6 months of treatment, this was increased to 60 mg of citalopram daily. She then started to have hallucinations, both auditory and visual. She continued to be depressed, and suicide was a risk for which she was admitted to the hospital for further management. She was also noted to be tremulous with unstable gait, and the neurology service was consulted. Further history obtained from family members revealed that she had gradual decreased ambulation and an increased need for assistance, with intermittent brief body jerks involving the arms and legs randomly, and not associated with alteration of consciousness. One month prior to this admission, she was found to be forgetful, and missed some important appointments, something unusual for her. She also had periods of confusion, but no history of seizures. There was no history of exposure to toxins, and she was only taking antidepressants. Neurological examination showed that she was alert and attentive but easily distracted, and was oriented only to

person. She described her mood to be low, but claimed to have no other problems. A few myoclonic jerks were noted, involving the upper extremities, and tremors were also seen, postural and kinetic, but not at rest. Memory examination showed a normal recall of immediately provided verbal and visual information (**Figures 1a & b**), but with impaired recall of that information after 5 minutes, even with cuing. She could recall information on history and general knowledge. Language examination showed impaired writing and comprehension, but normal fluency and repetition. There was also disturbance of executive functions (clock drawing) (**Figure 1c**). No apraxia or neglect was detected. Cranial nerves, motor, and sensory examinations were normal. She had ataxic gait, and kinetic tremors were noted with finger-nose and heel-shin testing. The differential diagnosis is shown in **Table 1**. Investigations revealed normal blood counts, serum electrolytes, coagulation profile, liver enzymes, vitamin B12, T3, T4 and thyroid stimulating hormone (TSH). Erythrocyte sedimentation rate was 4 (normal value <10) and C-reactive protein level was <0.2 mg/dl (normal value <1.0 mg/dl). Autoimmune screening (rheumatoid factor, antinuclear antibodies, anti-double stranded DNA antibodies, C3, C4, anti-SM antibodies, anti-SSA antibodies, anti-SSB antibodies, and anti-Jo 1 antibodies) and paraneoplastic antibodies (anti-Yo antibodies, anti-Hu antibodies, and anti-Ri antibodies) were negative, and serum and urine protein electrophoresis was also normal. Human immune deficiency virus (HIV) and Lyme serology were negative. A brain MRI showed diffuse signal changes involving the white matter bilaterally, and the anterior and posterior regions (**Figure 2**) with no contrast enhancement. Cerebral angiogram was normal. An EEG showed mild generalized slowing, with no periodic sharp waves seen. The CSF analysis results are shown in **Table 2**. Both CT of the chest and abdomen were normal, with no signs of occult malignancies. Serum concentration of antithyroid peroxidase antibodies was 320 IU/mL (reference level <60 IU/mL). Based on the clinical scenario, and the elevated serum antithyroid peroxidase antibodies and exclusion of other possible diagnoses, SREAT, or Hashimoto's encephalopathy was suspected. A trial of steroid therapy was initiated with methylprednisolone IV 1 gm daily for 3 days, followed by 60 mg of oral prednisone daily. She started to improve dramatically within days. She was more alert and oriented, and could recall new information after 5 minutes, with cuing at times. She

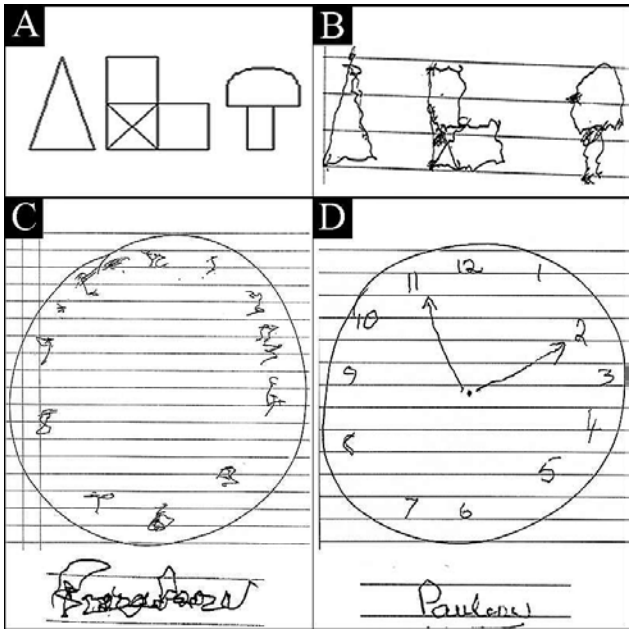

Figure 1 - Memory examination showing **A**) The geometric shapes used to test visual memory, which were shown for a short period of time. **B**) She was able to draw them immediately (immediate memory), but was unable to draw them after 5 minutes (short-term memory). Tremor was noted. **C**) She was asked to add all the numbers on a circle representing a clock face, and set the time to 10 minutes past 11. She was unable to perform the task. She was also asked to write her name below the circle. **D**) Following steroid therapy, she was asked to perform the same task as in **C**). Marked improvement was noted.

Table 1 - Differential diagnosis.

Infective encephalopathy
Creutzfeldt-Jakob disease
HIV encephalopathy
Neurosyphilis
Lyme disease
Cryptococcal meningitis
Progressive multifocal leukoencephalopathy
Cytomegalovirus encephalopathy
Inflammatory
Primary CNS vasculitis
CNS lupus
Sjögren's syndrome
Antiphospholipid syndrome
Sarcoidosis
Toxic/metabolic
Hashimoto's encephalopathy
B12 deficiency
Electrolyte disturbance (calcium, magnesium)
Bismuth/mercury/arsenic toxicity
Neoplastic
Primary CNS lymphoma
Intravascular lymphoma
Paraneoplastic encephalopathy
Brain metastasis
Neurodegenerative
Dementia of Lewy bodies
Fronto-temporal dementia
Psychiatric disorder

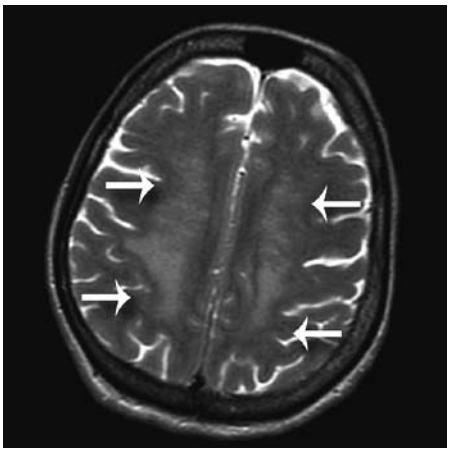

Figure 2 - Axial T2 brain MRI showing hyperintense signal changes (arrows) involving the subcortical white matter bilaterally.

Table 2 - Cerebrospinal fluid analysis results.

Variable	Results	Reference range
White cells	33 (95% lymphocytes)	<5
Red cells	0	0
Glucose	3.5 mmol/dL*	2-4.4 mmol/dL
Protein	940 mg/dL	450 mg/dL
Cultures	Negative	-
Oligoclonal bands	Present	Not detected
Protein 14-3-3	Not detected	Not detected
VDRL	Non reactive	Non reactive
Cytology	No malignant cells detected	-

*- serum glucose = 6.0 mmol/dL,
VDRL - Venereal Disease Research Laboratory

had normal language examination, including writing, with marked improvement in executive functions (**Figure 1d**). Over the next few months, her gait was normal, her mood improved markedly, and she returned to work. Her repeated antithyroid peroxidase antibodies level was 34 IU/mL. She maintained this improvement for over a year on 25 mg of prednisone daily.

Discussion. The incidence of late onset psychiatric symptoms, particularly depression, can be an indication of an underlying organic brain disease, either inflammatory or degenerative,[6] for which extensive workup is warranted. The reported psychiatric symptoms in SREAT include depression, mania, hallucinations, and psychosis. Our patient showed an interesting psychiatric presentation, a late onset depression and psychosis, which did not respond to therapy after 6 months of treatment. Furthermore, the progressive neuro-cognitive impairment raised red flags on the etiology of the depression, which cannot be claimed to be within the spectrum of major depression with psychosis. This scenario enforces the fact that organic brain diseases should be suspected in cases with late onset psychiatric presentation. One may speculate that the first stage of her presentation, the depression, was the earlier stage of thyroiditis, namely, hypothyroidism. She was tested for thyroid disease, as part of the screening for depression, and was found to be euthyroid, even at later stages. This indicates that the depression was indeed the first symptom of SREAT, and was the only symptom for 6 months prior to the disease progression. This may also suggest the need to include antithyroid antibodies when screening for depression in addition to the routine thyroid function test, but further research will be required to validate this.

The pathophysiology of SREAT is not fully understood. Neuropathological data in the literature showed perivascular lymphocytic infiltrates, resembling vasculitis.[7] However, the presence of other auto-immune diseases and improvement following the immune therapy, indicate the autoimmune nature of the disease. Due to the rarity of this syndrome, it is not easy to fully understand the exact nature of the disease, which could contribute to better outcomes.

Anti-thyroid antibodies are linked to thyroiditis, and all patients with high concentrations of the antibodies have pathologic evidence of thyroiditis. The association between the stages of thyroiditis (namely, hypo-, eu-, or hyperthyroidism) and SREAT is not clear, since SREAT is observed at any stage. Hence, the use of standard thyroid function test alone is not sufficient to predict SREAT. More importantly, the use of anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies is essential, in suspected cases, to diagnose SREAT.[4] However, patients with autoimmune thyroiditis, who were euthyroid with the absence of encephalopathy, were reported to have abnormal brain SPECT scan,[8] suggesting a higher incidence CNS involvement in cases of autoimmune thyroiditis.

Differentiating between myxedemic coma and coma caused by SREAT can be challenging. Features favoring the former include the presence of hypothermia, hyponatremia, and hemodynamic instability, with a history of precipitating factors such as exposure to cold, sepsis, gastrointestinal hemorrhage, burns, surgery or drugs. A thyroid function test in myxedemic coma shows elevated TSH, low T3 and T4 levels, and a normal thyroid function test in such cases will exclude myxedemic coma, but will not rule out SREAT. More importantly, myxedemic coma is more common than SREAT, and is easier to diagnose, yet differentiating these conditions is critical since therapy of the 2 conditions differ.

Rapidly progressive cognitive decline can have a wide differential diagnosis (**Table 1**). Classically, neurodegenerative diseases such as Creutzfeldt-Jakob disease (CJD) is the working diagnosis, especially in association with myoclonus. Our patient presented with a clinical syndrome similar to CJD, and in fact, cases of SREAT have been misdiagnosed initially with CJD.[5]

Differentiating the 2 diseases may not be an easy task, but the presence of high titers of antithyroid antibodies and improvement following steroid therapy strongly favors the diagnosis of SREAT. Other ways to differentiate the 2 diseases are the presence of protein 14-3-3 in the CSF or periodic sharp waves on EEG, both of which are markers of CJD in the presence of the proper clinical settings, in addition to the typical neuropathological changes seen in CJD. Efforts should be made to differentiate the 2 diseases, since the prognosis is dismal in CJD, while SREAT usually has a benign natural history.

Efforts have been made to propose a diagnostic criteria for SREAT.[9] The clinical features, on which the criteria was based, are encephalopathy (cognitive decline, either slow or rapidly progressive, seizures, hallucinations, psychosis, or mood changes) or stroke-like episodes, both of which could have a relapsing-remitting pattern, in addition to nonspecific abnormalities on EEG and brain MRI, the presence of high antithyroid antibodies titers, and exclusion of other possible etiologies. The response to steroid therapy was not observed in the first described case by Brain et al,[1] although there was a consistent response to steroid therapy in reported patients in the literature, including the dramatic response in our patient. Long-term follow up has also shown relapse in some patients following withdrawal from steroids.

The MRI changes were observed and included nonspecific cerebral atrophy, signal changes in the subcortical and periventricular white matter, or dural enhancements. Some of these changes may persist after treatment. Around half of the patients may have a normal brain MRI.[1] The EEG usually shows generalized slowing that correlates with the degree of encephalopathy, which resolves following clinical improvement.[10] This supports the key role of EEG in monitoring disease course. The EEG can also play a vital role in excluding other etiologies, particularly CJD. The CSF profile usually shows elevated white cells and negative bacterial and viral cultures. Proteins are usually elevated, and oligoclonal bands are infrequently present. Cases with elevated CSF antithyroid antibodies have been reported.[11]

In conclusion, SREAT, or Hashimoto's encephalopathy, is an important diagnosis to be considered in the presentation of encephalopathy or stroke-like episodes, as well as rapidly progressive dementia, since this is a treatable, but also life-threatening disease. Consequently, failure to identify patients with high antithyroid antibodies, who have a clinical profile consistent with SREAT, will lead to the wrong diagnosis and unnecessary impact on the patient and family. Increased awareness of SREAT by neurologists, endocrinologists, and internists will help to identify patients and better understand the disease.

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