It also has been argued that myosin degradation, which affects only some muscle fibers, cannot explain the severe weakness and paralysis usually observed in these patients. The authors also noted in a rat model of the disease that the loss of excitability can be related to three main processes: increased sodium channel inactivation, persistent expression of chloride conductance, and reduction of sodium conductance, which could be secondary to a decreased density of the sodium channels. No data are available, however, regarding the molecular mechanism underlying these electrophysiologic findings.

Acute quadriplegic myopathy is probably a much more frequent condition than was previously believed. In a recently published study on patients who underwent liver transplantation, Campellone et al. reported that about 9% of the patients displayed the features of acute quadriplegic myopathy. Situations such as sepsis and renal or respiratory failure are often associated with severe acidosis, and also with high levels of cytokines, some of which, for example tumor necrosis factor-α could have a catabolic effect on muscle. These could be an important trigger in the pathogenesis of acute quadriplegic myopathy.

On the whole, these data suggest that acute quadriplegic myopathy is a disorder of the protein turnover in muscle. Several independent factors, such as corticosteroids, immobilization, and cytokines, associated with severe systemic disease could concur to trigger a cascade of events leading to the excessive, but still somehow controlled, activation of specific protein degradation pathways. This could cause the selective degradation of specific muscle proteins, that is myosin thick filaments and possibly some as yet unidentified components of the sarcolemma, thus causing loss of excitability (Figure 4). Both adult and child neurologists must be aware of this condition in order to establish a correct prognosis and initiate physical therapy as soon as possible to reduce complications in these patients.

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Encephalopathy as the Presenting Symptom of Hashimoto’s Thyroiditis

ABSTRACT

In recent years, encephalopathy has increasingly been recognized as a complication of Hashimoto's thyroiditis. It can begin abruptly as a stroke-like event, acute seizures, or confusion, or as an insidious decline in cognitive function. Most reported cases have been on adult patients, although this encephalopathy does affect children as well. This form of encephalopathy should be considered...
in the differential diagnosis of children and adults with unexplained neurologic deterioration. We describe the case of a child in whom acute encephalopathy was the presenting symptom of Hashimoto's thyroiditis. (J Child Neurol 2000;15:66-69).

Thyroid disease has long been recognized as a cause for diverse neurologic impairments, including dementia, psychosis, and coma. A particular form of encephalopathy, often occurring in euthyroid individuals, has been increasingly associated with Hashimoto's thyroiditis, and can be the presenting symptom of this form of thyroiditis. Neurologists frequently face previously healthy patients with acute or subacute onset of cognitive deterioration, seizures, myoclonus, and coma. It is important to consider this form of encephalopathy as a potential etiology in some of these cases. We describe a child with bouts of sudden, unexplained encephalopathy, who was diagnosed with Hashimoto's thyroiditis.

Case Description

A 9-year-old girl was brought to the emergency room after a generalized tonic-clonic seizure, followed by confusion and agitation. She received one dose of intravenous diazepam on her way to the emergency room. She had been treated for seizures several weeks earlier and had been healthy since. The general examination was normal, with no localizing neurologic findings. Agitation and confusion persisted, the patient was intubated, and ventilatory support began, and she was admitted to the intensive care unit. Acyclovir and ceftriaxone were administered. Laboratory tests, including full blood count, electrolytes, kidney function tests, aminotransferases, calcium, and magnesium, were normal. Cerebrospinal fluid analysis revealed 0 to 1 leukocytes/µL, glucose 52 mg/dL, and protein 95 mg/dL. Opening pressure was 18 cm of water. Blood, cerebrospinal fluid, and urine cultures were negative. Viral cultures of pharynx, nasopharynx, and cerebrospinal fluid were negative, and Enterovirus was isolated in stools. Mycoplasma pneumoniae antibodies were not detected. There was no evidence of toxic ingestion in the gastric contents or urine screening. Epstein-Barr and herpes simplex virus infection were also ruled out.

Electroencephalogram (EEG) demonstrated diffuse high-amplitude 3- to 4-Hz activity, without epileptiform discharges. Head computed tomography and magnetic resonance imaging (MRI) with and without contrast media were normal. After 2 days of confusion and lethargy the patient quickly regained full consciousness. However, she remained somewhat disoriented and emotionally labile but continued to improve and was discharged home 6 days after admission. Her school performance did not return to baseline, and she was somewhat inattentive for the next several weeks (previously she had been an excellent student). A repeat EEG was normal 1 month later.

Ten weeks after the first hospitalization the patient was re-admitted with a generalized convulsion, followed by confusion and lethargy for 3 days. During this admission hypothyroidism was diagnosed, and thyroid enlargement was detected. Antimicrosomal antibody titer was 1:1,638,400 (normal = negative), antithyroglobulin antibodies were not detected, and a diagnosis of Hashimoto's thyroiditis was established. EEG showed diffuse slowing of background activity in the theta range. Blood count and chemistry were normal; cerebrospinal fluid protein was 94 mg/dL. Ammonia level was normal. Repeat brain MRI was normal. The patient was discharged 6 days later on thyroid replacement therapy. At her next clinic visit 2 months later she was reported to act less maturely than before, and still was not performing at her pre-illness level at school. A repeat EEG was normal. After this visit the patient did not return to follow-up.

Discussion

Hashimoto's thyroiditis is the most common form of thyroiditis in children and adults. It is characterized by insidious, symmetric enlargement of the gland with few or no local neck symptoms, and it can lead to hyperthyroidism and thyrotoxicosis. It occurs predominantly in females, and it is the most common cause of thyroid enlargement and hypothyroidism in children over 6 years of age in North America. It is estimated that 3% to 4% of the adult population suffers from this form of thyroiditis.3,4 Neurologic manifestations of thyroid disease are well recognized, and include dementia, psychosis, cerebellar ataxia, and myxedema coma.5,6 Encephalopathy has been reported increasingly in patients with Hashimoto's thyroiditis. This neurologic complication more commonly occurs in euthyroid patients, suggesting a nonmetabolic pathophysiologic mechanism.5,6-8

Although most reported patients have been adults, patients as young as 12 years of age have been described. Ninety percent were women.3 The most common symptoms during acute relapses were coma and stupor; agitation, seizures, localized motor deficit, tremor, ataxia, and myoclonus. A few patients demonstrated mild cognitive deficits for up to 30 months after the onset of symptoms.7-13 Based on their own experience with six patients and 14 well-documented cases in the medical literature, Rothbauer-Margreiter et al noted two different clinical presentations, with some symptom overlap. In approximately 35% of cases a vasculitis-like picture occurred, involving stroke-like episodes, with or without mental or consciousness changes. The remaining two thirds of patients presented with an insidious, diffuse picture of progressive cognitive deterioration, dementia, lethargy, and coma. Partial and secondarily generalized seizures, myoclonus, and tremor occurred more often in the latter group.5 It remains to be seen whether different pathogenetic mechanisms are responsible for these two clinical presentations.

Little information is available on the natural course of untreated encephalopathy in patients with Hashimoto's thyroiditis. When treated, the disease follows a chronic course characterized by acute relapses with full neurologic recovery between attacks, and eventual symptom disappearance within months to 2 years.5,8,11,12,14-17 Most of the available information relates to patients treated with corticosteroids and other immunosuppressive agents.

The pathophysiology of encephalopathy in patients with Hashimoto's thyroiditis is poorly understood. Several possible mechanisms have been suggested: endocrine derangement, autoimmune process, and vasculitic phenomena. Most reported patients have been euthyroid or with normalized thyroid function while on hormone replacement therapy. Furthermore, the few described patients who have been hypothyroid at the time of first presentation suffered relapses while on thyroxine replacement therapy.8,13 Autoimmune disease is present in about 25% of patients with Hashimoto's thyroiditis. Associated illnesses include pernicious anemia, rheumatoid arthritis, myasthenia gravis, lupus erythematosus, insulin-dependent diabetes mellitus, and ulcerative colitis.14,15 At least five antigen-antibody systems have been identified involving different constituents of the thyroid gland: thyroglobulin, microsomal antigen (thyroperoxidase), a cell surface antigen, a thyrotropin receptor antibody, and antibodies against thyroid hormones themselves.5 In clinical practice, thyroid antibodies assayed are the microsomal antibody and the thyroglobulin antibody.1 In patients with Hashimoto's thyroiditis associated encephalopathy,
cerebrospinal fluid oligoclonal bands were positive in 4 of 15 cases, and in one patient with pernicious anemia, distal renal tubular acidosis, and recurrent encephalopathy, the cerebrospinal fluid synthesis of IgG was increased, suggesting an autoimmune process. Interestingly, all four patients with positive oligoclonal bands had higher antimicrosomal antibody titers (greater than 1:100,000) than the negative cases. Nevertheless, antibodies against brain tissue have not been identified. An important step in determining the pathophysiology of this recurrent form of encephalopathy would be the recognition of the mechanisms associated with the relapsing nature of this condition.

The third proposed mechanism is cerebral vasculitis. The elevated erythrocyte sedimentation rate, the stroke-like events described in some patients, and the good clinical response to glucocorticosteroids would suggest a transient angiitis. However, cerebral angiography has been normal in 10 reported cases. Brain MRI has been normal or has shown nonspecific cortical atrophy in reported cases. However, in two patients transient white-matter abnormalities have been noted using fluid-attenuated inversion-recovery sequences. Another patient showed a focal area of increased $T_2$ signal in the left frontal subcortical white matter. These findings resolved with high-dose corticosteroid treatment. Furthermore, postmortem results on the initial patient with a stroke-like clinical picture reported by Brain et al showed no macroscopic evidence of previous strokes. However, single photon emission computed tomography (SPECT) scanning in a 59-year-old woman revealed bilateral, symmetric, temporal, parietal, and frontal hypoperfusion associated with progressive cognitive deterioration and myoclonus. A subsequent SPECT study was normal following clinical improvement with thyroid hormone replacement therapy. The authors postulate a diffuse disruption of cerebral microvasculature secondary to autoantibody or immune complex deposition as the mechanism for the clinical and SPECT findings.

EEG recordings during episodes of encephalopathy usually show nonspecific diffuse slowing. Most EEG recordings have been obtained during clinical exacerbations. However, occasional studies performed up to 2 to 3 weeks after an acute episode of encephalopathy have shown marked improvement in the EEG background activity, as seen in our patient. Cerebrospinal fluid analysis demonstrates elevated protein in 75% of cases; 25% of these patients also had mild mononuclear pleocytosis. Antithyroglobulin antibodies are positive in more than 55% of patients with Hashimoto’s thyroiditis and antithyroid microsomal antibodies in 95% of cases. The latter show a better correlation with histologic thyroiditis than do antithyroglobulin antibodies. Antibody levels are not a reflection of thyroid function but do indicate significant autoimmune thyroid disease. Low levels are present in other diseases, but high levels are indicative of lymphocytic infiltration of the thyroid gland. Serum antibody concentrations decrease on thyroid hormone replacement, and generally are unmeasurable after several years of therapy.

Encephalopathy in Hashimoto’s thyroiditis occurs more commonly in euthyroid patients, and in general, there is no correlation between antibody level and clinical status. Among the 20 patients summarized by Rothbauer-Margreiter et al, 18 had normal thyroid function when the encephalopathy became evident. Since thyroid function is frequently evaluated in the work-up of demented and psychotic patients, the diagnosis of Hashimoto’s thyroiditis could be delayed or missed if the clinician is not aware that most cases are euthyroid. Antimicrosomal and antithyroid antibodies should be measured in every patient presenting with acute or subacute unexplained encephalopathy.

Glucocorticosteroids, particularly dexamethasone, methylprednisolone, and prednisone have been effective in reversing the symptoms of Hashimoto’s thyroiditis encephalopathy. Since controlled trials have not been performed, treatment regimens have so far been empirical, ranging in duration between 2 and 10 years. Although there has been no correlation between duration of symptoms and corticosteroid response, it appears that patients with acute vasculitis-like symptoms respond faster and better than those with diffuse progressive encephalopathy. Anecdotally, in most treated cases cerebrospinal fluid protein and cell count, antithyroid antibodies, and EEG background activity have normalized as clinical symptoms improved. Relapse has occurred in some patients following corticosteroid discontinuation. In some of these cases cyclophosphamide and azathioprine have been effective as adjunctive therapy.

Encephalopathy associated with Hashimoto’s thyroiditis is being increasingly recognized as a cause of acute and subacute neurologic impairment. Hashimoto’s thyroiditis is a common disease that can go unrecognized for long periods because many patients do not depict abnormal thyroid function or overt thyroid enlargement. Since it responds to corticosteroid therapy, a high index of suspicion is needed when evaluating a patient with unexplained stroke-like symptoms, or intermittent or progressive encephalopathy.

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