Background: Hashimoto encephalopathy is a potentially fatal condition associated with a presentation of myoclonus, altered conscious state, strokelike episodes, rapid cognitive decline, and neuropsychiatric symptoms. Both congenital hypothyroidism and acquired hypothyroidism are common in patients with Down syndrome.

Objective: To describe the presentation of Hashimoto encephalopathy in patients with Down syndrome.

Design: Clinical case reports.

Setting: General neurology unit.

Patients: Two Down syndrome patients diagnosed as having Hashimoto encephalopathy are described.

Intervention: High-dose oral corticosteroids.

Main Outcome Measures: Neurologic examination, electroencephalography, and blood analysis results.

Results: Both patients responded to treatment, with a slow return to their premorbid level of function.

Conclusion: Hashimoto encephalopathy should be considered in Down syndrome patients with rapidly progressive cognitive decline.

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Hashimoto Encephalopathy

Hashimoto encephalopathy, also known as steroid-responsive encephalopathy associated with autoimmune thyroiditis, is a potentially fatal condition associated with a presentation of myoclonus, altered conscious state, strokelike episodes, rapid cognitive decline, and neuropsychiatric symptoms, including psychosis, hallucinations, and abulia. It is an important differential diagnosis of rapidly progressive dementia. It is also an important cause of potentially reversible dementia because with prompt and appropriate treatment its symptoms can be completely reversed. Controversially, Hashimoto encephalopathy can present in the absence of associated thyroid function abnormalities, even though it is associated with high titers of antithyroid peroxidase and antithyroglobulin antibodies. Both congenital hypothyroidism and acquired hypothyroidism are common in patients with Down syndrome, with an estimated community prevalence varying from 9% to 35%. Hashimoto thyroiditis is the most common acquired cause in this population, causing 30% to 93% of cases of hypothyroidism and varying with the age of diagnosis of thyroid disease. Physicians routinely test thyroid function in patients with Down syndrome who present with functional decline. Cognitive decline in euthyroid patients is often attributed to the onset of Alzheimer disease, known to have an early onset in association with trisomy 21.

In this article, 2 euthyroid Down syndrome patients diagnosed as having Hashimoto encephalopathy are described. One had a history of hypothyroidism but had been receiving maintenance levothyroxine sodium for many years. Both responded to empirical high-dose prednisolone therapy with a gradual wean, slowly returning to their premorbid level of function.

Report of Cases

Patient 1

A 22-year-old woman with Down syndrome presented with a 9-month history of functional decline, myoclonic jerks, increased anxiety, and behavioral change. Thyroid function was normal. Her level of function had markedly worsened during...
the preceding 2 months, with increasing weakness, reduced verbal output, increased somnolence, possible visual hallucinations, and leg jerks. During the 4 weeks before hospital admission she had required assistance with all of her activities of daily living. She had presented to the emergency department 1 month before admission with altered thinking and behavioral change. A possible underlying psychosis was considered. Risperidone, 2 mg/d, was administered and later venlafaxine hydrochloride, 150 mg, was added in view of a possible diagnosis of depression. Despite these therapies, she presented 1 month later for investigation of worsening level of function and increasing jerks.

Vital signs were normal. Neurologic examination revealed marked bradyphrenia and abulia, with a positive glabellar tap and palpomental reflexes but no grasp reflex. The patient was poorly cooperative, and no higher mental function testing could be performed. The results of cranial nerve examination were normal. There was evidence of mild hypertonia and hyperreflexia in her lower limbs. Limb power, sensation, and coordination were intact. Frequent bilateral arm and, to a lesser extent, leg myoclonic jerks were noted throughout the examination.

Admission electroencephalography (EEG) revealed a background of admixed polymorphic θ and δ, consistent with a diffuse encephalopathic process (Figure 1). Magnetic resonance imaging of the brain revealed brachycephaly but no significant cortical or white matter lesions (Figure 2). The results of basic blood analyses were normal, including a normal vitamin B₁₂ level (590 pg/mL; reference range, 187-1059 pg/mL [to convert to picomoles per liter, multiply by 0.7378]), and she was euthyroid (thyrotropin, 2.90 mIU/mL; free thyroxine, 1.0 ng/dL [to convert to picomoles per liter, multiply by 12.871]; free triiodothyronine, 240 pg/dL [to convert to picomoles per liter, multiply by 0.0154]; all within the reference range for our laboratory). Lumbar puncture revealed a bland cerebrospinal fluid: lymphocytes, 1; red blood cells, 0; protein, 0.02 g/dL; and glucose, 59 mg/dL. The results of the cerebrospinal fluid herpes simplex virus polymerase chain reaction were negative. Test-

Figure 1. Serial electroencephalograms from patient 1. A double banana montage is shown; the same filter settings were used for each for comparison. Note the improvement in background rhythm from a diffuse encephalopathic state to normal α rhythm.

Figure 2. Brain images of patients 1 and 2. T1 (A) and T2 (B) images are shown. Patient 1 underwent axial magnetic resonance imaging at the level of the basal ganglia. There was evidence of brachycephaly but no atrophy. Patient 2 underwent noncontrast axial computed tomography at the level of the basal ganglia (top). Two sections (bottom) shown demonstrate widespread atrophy. Note the incidental basal ganglia calcification.
ing for autoantibodies revealed an antinuclear antibody titer of 1:640. A diagnosis of Hashimoto encephalopathy was considered: her antithyroid peroxidase antibody level was 132 IU/mL (reference range, <35 IU/mL), and her antithyroglobulin antibody level was 976 IU/mL (reference range, <40 IU/mL). A diagnosis of Hashimoto encephalopathy was made, and treatment commenced.

She was administered oral prednisolone, 75 mg/d (1.5 mg/kg), without prior intravenous dosing. Her myoclonus improved during the next 24 hours, and staff and family noted increased alertness and cooperation during the 72 hours after treatment. Rapid functional gains were made on the ward, and 14 days after commencing oral prednisolone therapy she was discharged home with a slowly weaning prednisolone regimen. Slow incremental gains in her cognition and function were made during the next 7 months. Her EEG normalized during a period of 12 months (Figure 1) as did her autoantibody levels (antithyroid peroxidase antibody, <10 IU/mL; antithyroglobulin antibody, 31 IU/mL). Low-dose maintenance prednisolone therapy had been given during this time.

On review 8 months after initiation of corticosteroid therapy, she was fully oriented. Results of her neurologic examination were normal, with no evidence of hypertonia, hyperreflexia, or myoclonus. She had returned to her normal level of function, including a return to her workplace 5 days a week.

PATIENT 2

A 46-year-old woman with Down syndrome was admitted with a 6-week history of increasing drowsiness, behavioral change, and twitching. Her history included hypothyroidism and probable early-onset Alzheimer disease, diagnosed on a background of 1 to 2 years of gradual functional and cognitive decline that necessitated transfer to a nursing home. Before her recent illness she was able to transfer from bed to chair and chair to walking frame and walk short distances with a gutter-frame with assistance. She was incontinent of urine. Her medications were valproate sodium, 200 mg 3 times daily, and thyroxine, 100 µg/d.

During the preceding 6 weeks, her mobility had markedly declined. She became dependent in all of her activities of daily living, incontinent of feces and urine, and wheelchair bound. She had ceased to verbalize or even attempt to communicate with staff. Her family reported that she always seemed confused. In the 2 weeks before hospital admission, increasing drowsiness and whole-body twitching had developed, which occurred for most of her waking hours. She developed some right-sided weakness and difficulty with swallowing and was noted to choke on her foods. Admission was arranged for treatment of nonconvulsive status epilepticus and consideration for insertion of a percutaneous endoscopic gastrostomy tube. Nasogastric tube feeding was commenced on the ward.

On admission, her blood pressure was 120/60 mm Hg and her heart rate was 90/min. She was afebrile, with a Glasgow coma scale score of 9. The patient was intermittently drowsy and uncommunicative. She was unable to follow simple commands. She appeared to be moving her left side more than the right. Higher mental function testing was not performed. The results of cranial nerve examination were within normal limits. Generalized limb hypertonia and hyperreflexia were noted. Her plantar reflexes were extensor, and intermittent myoclonus was seen in all limbs.

The results of basic blood analyses were normal, including a C-reactive protein level less than 0.21 mg/L (to convert to nanomoles per liter, multiply by 9.524) and a vitamin B12 level of 689 pg/mL. The results of thyroid function testing were consistent with adequate thyroxine replacement (thyrotopin, 3.39 mIU/L; thyroxine, 1.3 µg/dL [to convert to nanomoles per liter, multiply by 12.871]). Her EEG revealed a background of high-amplitude polymorphic 8 with high-amplitude triphasic waves. Frequent myoclonic jerks in the absence of associated cortical activity were noted. Computed tomography of the brain revealed generalized atrophy consistent with her earlier diagnosis of Alzheimer disease and bilateral basal ganglia calcification (Figure 2). Autoantibody testing revealed an antithyroid peroxidase antibody titer of 87 IU/mL and a normal antithyroglobulin antibody level (<20 IU/mL; reference range, <40 IU/mL). A diagnosis of probable Hashimoto encephalopathy was made, and no further serologic or cerebrospinal fluid studies were performed.

Intravenous methylprednisolone, 500 mg, was given for 3 days. Within 24 hours of treatment initiation her jerking stopped, with only some small twitches observed. Increased alertness was noted 72 hours after treatment. Five days after commencement of corticosteroid, her nasogastric tube was removed and oral intake commenced, with rapid return to her premorbid diet. Her family members commented on increased interaction and cooperation. She was started on a trial of reconditioning physiotherapy but was still transferring with the 2-person assist or hoist transfer. Eleven days after commencement of treatment, she was discharged back to her nursing home with a prescription for 50 mg/d of oral prednisolone with a plan to gradually wean this dose. Fecal continence was regained.

On review 3 months after discharge, she had returned to her normal level of communication and oral intake. She was alert but not obeying simple verbal commands. Neurologic examination was limited but revealed no evidence of myoclonus, hypertonia, or hyperreflexia. Plantar responses were flexor. Her thyroid antibody level had returned to the reference range.

COMMENT

The association of Hashimoto encephalopathy with Down syndrome has not been previously described. Two patients with Down syndrome are described, both with a clinical presentation of Hashimoto encephalopathy diagnosed on the basis of a history of myoclonus, rapid cognitive decline, abnormal EEG, and positive antithyroid peroxidase antibody titers. Both patients were euthyroid and had a rapid response to corticosteroid therapy,
with early resolution of myoclonus and slow return to their premorbid level of function. In the patient followed up with serial EEGs, this was associated with normalization of the recording from a background of θ and δ to normal reactive α rhythm.

Alzheimer disease is often considered in Down syndrome patients who present with functional decline, with patients presenting in their fourth or fifth decades of life. High levels of β-amyloid deposition by the fourth decade in this patient population are well described. A number of factors influence the age at onset of cognitive decline, including susceptibility genotypes, atypical karyotypes, and estrogen deficiency. However, alternative diagnoses, such as thyroid dysfunction, should be considered in younger patients and those who present with a rapid onset of functional decline. Alzheimer disease usually has an insidious onset and gradual progression and is not usually associated with altered conscious state, early seizures, focal neurologic abnormalities, and myoclonus.

Although rare, the association of Hashimoto encephalopathy in patients with Down syndrome is not surprising given the high incidence of autoimmune thyroid disease in this population. Even in the setting of normal thyroid function, thyroid antibody levels should be measured and the diagnosis of Hashimoto encephalopathy considered in patients with Down syndrome who present with rapid cognitive decline, particularly in association with myoclonus and an abnormal EEG result.

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Correspondence: Amy Brodtmann, MD, PhD, National Stroke Research Institute, Level 1, Neurosciences Building, Austin Health, Heidelberg 3084, Australia (amyb@alphalink.com.au).

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