

Steroid-responsive Thalamic Lesions Accompanying Microbleeds in a Case of Hashimoto's Encephalopathy with Autoantibodies Against α -enolase

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Abstract

A 67-year-old man receiving antithrombotic therapy developed rapidly progressive amnesia. T2-weighted images of brain MRI revealed hyperintense lesions in the bilateral thalamus accompanied by microbleeds. Antithyroglobulin antibodies and autoantibodies against the N-terminal of α -enolase (NAE) were identified in the patient's serum; therefore, Hashimoto's encephalopathy (HE) was suspected. Although the patient's radiological findings improved following steroid therapy, his symptoms did not improve, possibly due to increased thalamic microbleeds. Because anti-NAE antibodies are possibly associated with vasculitis, HE accompanied by anti-NAE antibodies may be exacerbated by microbleeds in patients receiving antithrombotic therapy.

Key words: α -enolase, antithyroid antibodies, Hashimoto's encephalopathy, microbleed, steroid-responsive encephalopathy, thalamus

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Introduction

Hashimoto's encephalopathy (HE), a neurologic complication of autoimmune thyroiditis, occurs independently of the thyroid status and is also termed 'steroid-responsive encephalopathy associated with autoimmune thyroiditis.'

Since Brain et al. (1) described the first case of HE, there has been debate about its nature despite the accumulation of data provided by more than 120 reported cases. The relationship between antithyroid antibodies and steroid-responsive encephalopathy is subject to considerable debate. Because the clinical features vary, two subtypes of HE have been proposed: (i) a vasculitic type, characterized by stroke-like episodes; and (ii) a diffuse progressive type, characterized by dementia or psychiatric disorders (2). Although autoimmune mechanisms may underlie the pathogenesis, the precise cause of HE remains unclear. Autoimmune cerebral vasculitis is likely because neuropathological examinations

of biopsy and autopsy specimens have shown lymphocytic infiltration into the walls of arterioles and venules in brain parenchyma (3, 4) and leptomeninges (4). Recently, Yoneda and colleagues reported that serum autoantibodies against the N-terminal region of α -enolase (NAE) are a useful diagnostic marker for HE (5). Because α -enolase is expressed in vascular endothelial cells, autoantibodies against α -enolase may be associated with vasculitic processes in the central nervous system in patients with HE.

We herein report the case of a patient with HE who demonstrated marked bilateral, symmetrical, hyperintense thalamic lesions on T2-weighted images that were concomitant with microbleeds. The presence of microbleeds within these lesions supports the possibility that vascular pathological processes contribute to the pathogenesis of HE.

Case Report

A 67-year-old man rapidly developed concentration and

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memory disturbances two weeks prior to admission. He had a medical history of hypertension, coronary heart disease, arterial fibrillation and chronic renal failure for which he was undergoing hemodialysis. He had been receiving both anticoagulant and antiplatelet therapies to prevent vascular events. In addition, he had been receiving antihypertensive therapy, and his blood pressure levels were well-controlled. Five days prior to admission, brain MRI showed increased T2-weighted signals in the periventricular white matter suggestive of small vessel disease. Although there were atrophic changes in both frontal lobes, no abnormal findings that could account for the patient's symptoms were apparent. He had a score of 30 on the Mini-Mental State Examination (MMSE). Because his symptoms were rapidly progressive, he was admitted to our hospital.

On admission, the patient was apathetic and exhibited disorientation and amnesia. His concentration and memory were impaired, and disinhibition of behavior was apparent. His cranial nerves were intact, and there were no meningeal signs. He demonstrated flapping tremors in both hands; however, the remainder of the neurological examination results were normal. The patient's MMSE score had deteriorated to 23. Electroencephalography revealed minor diffuse slow-wave activity (8 Hz) with no epileptic discharges. A cerebrospinal fluid (CSF) examination showed an increased protein concentration (81 mg/dL) without pleocytosis. No oligoclonal IgG bands were found in the CSF. The CSF titers of antibodies against herpes simplex and varicella-zoster virus were normal. Although the patient had chronic renal failure, all other laboratory values, including peripheral blood parameters, liver function test results, the serum ammonia concentration and vitamin the B1 and B12 concentrations, were normal. The levels of serological markers for collagen disease, including antinuclear, anti-DNA, anti-SS-A/SS-B, antineutrophil cytoplasmic and myeloperoxidase-antineutrophil cytoplasmic antibodies, were within the normal ranges. Serologic tests for syphilis and human immunodeficiency virus were also negative. In addition, we also checked for autoantibodies associated with paraneoplastic neurological syndrome (*ravo* PNS Blot; *ravo* Diagnostika GmbH, Freiberg, Germany); however, these autoantibodies (anti-HuD, Yo, Ri, CRMP5, amphiphysin, Ma1 and M2 antibodies) were not detected. Although the serum concentrations of thyroxine, thyrotoxine and thyroid-stimulating hormone were normal, the serum concentration of antithyroglobulin antibodies was increased (56.2 U/mL; normal, < 28 U/mL). However, tests for other antithyroid antibodies were normal. Further brain MRI showed bilateral markedly hyperintense lesions in the thalamus on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images (Fig. 1A, B). There were also bilateral hyperintense thalamic lesions on diffusion-weighted images (DWI) that had a dark appearance on apparent diffusion coefficient (ADC) mapping (Fig. 1C, D). The thalamic lesions were accompanied by hypointense lesions on T2* imaging (Fig. 1E). A sagittal section of an enhanced computed tomography image showed

no filling defects in the proximal straight sinus (Fig. 1F).

Because we suspected HE, we prescribed high-dose methylprednisolone (1,000 mg i.v.) therapy for three days. Immediately thereafter, the patient's symptoms and MRI findings markedly improved (Fig. 2A). However, his symptoms subsequently deteriorated, and another MRI showed enlargement of the bilateral thalamic lesions (Fig. 2B). Although we again prescribed high-dose methylprednisolone therapy, the patient was less responsive to the second course. Five weeks after admission, the serum autoantibodies against NAE became positive. We prescribed high-dose methylprednisolone therapy an additional three times, and some radiological improvement in the bilateral thalamic lesions was identified thereafter (Fig. 2C). Following the completion of high-dose methylprednisolone therapy, the patient was treated with oral prednisolone (60 mg/day) followed by an oral taper. His symptoms partially improved and he exhibited a slightly improved MMSE score of 26; however, his memory did not recover completely, possibly owing to increased thalamic microbleeds (Fig. 2D).

Discussion

We herein reported a case of HE with unusual thalamic lesions on MRI. The unusual aspects of the radiological findings were that the lesions were bilateral and localized symmetrically in the thalamus. Marked improvement in these lesions following repeated steroid pulse therapy indicated that the lesions were caused by an immune process, which is consistent with a diagnosis of HE. Increased serum antithyroglobulin antibodies and a normal thyroid function indicated Hashimoto's thyroiditis with euthyroidism. Furthermore, the subacute onset and steroid responsiveness shown on MRI were consistent with a diagnosis of HE. In addition, the presence of serum antibodies against NAE, which is a recognized diagnostic marker for HE (5), supported this diagnosis in our patient. Our patient met the diagnostic criteria for HE proposed by Schauble et al. (6) despite the fact that his cognitive function did not improve after treatment with prednisolone. Although a pathological evaluation performed to make the differential diagnosis of neuro-Behcet's disease was lacking, we found no clinical characteristics of Behcet's disease, such as oral ulcerations, headaches, fever, urogenital ulcerations or uveitis.

The feature of the present case that was not characteristic of HE is that our patient's symptoms failed to fully improve following treatment with steroid therapy. Although the hyperintense lesions on both T2-weighted and FLAIR images improved after treatment with high-dose methylprednisolone, the small hypointense lesions on T2* images in both thalamus became increased. These thalamic lesions were suggestive of microbleeds, which would explain why our patient's symptoms failed to improve fully after treatment with high-dose methylprednisolone. Several lines of evidence suggest that thalamic lesions caused by vascular disorders are associated with cognitive dysfunction (7).

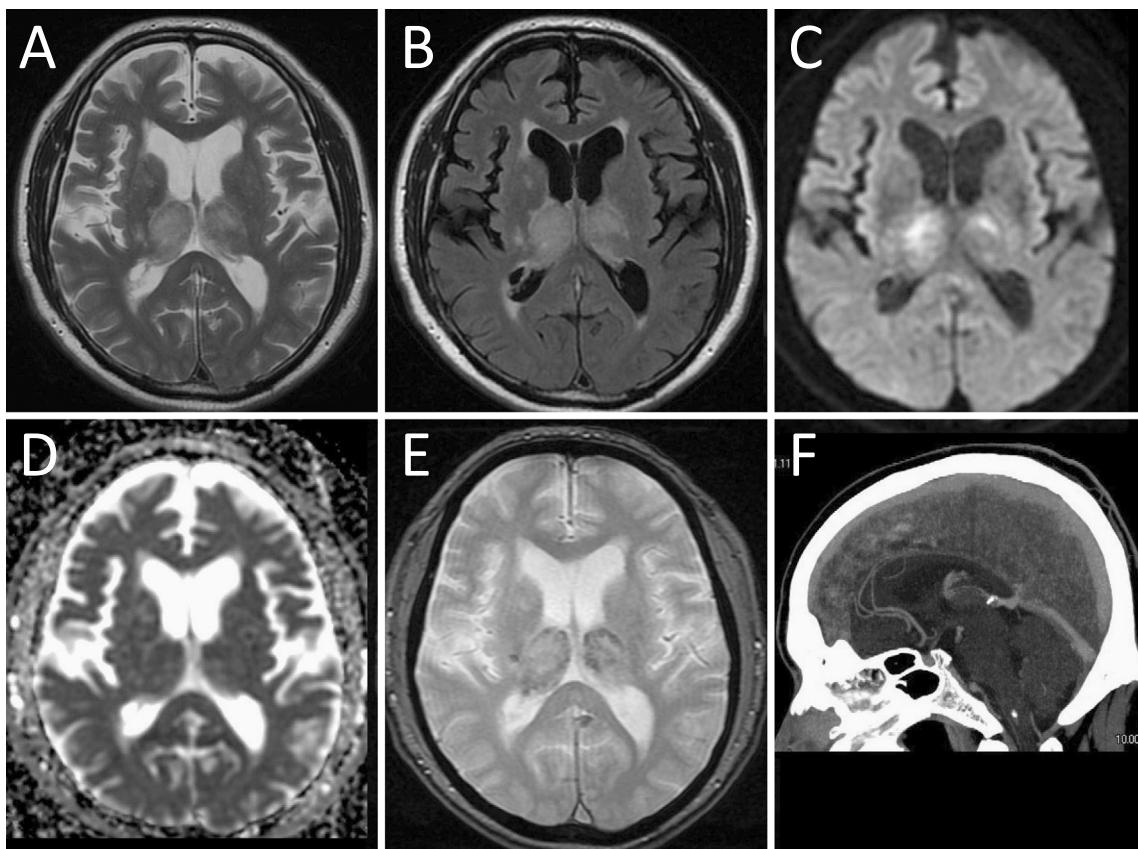


Figure 1. MRI and enhanced CT of the brain obtained one day after admission. Hyperintense lesions with focal edema are present in the bilateral thalami on axial T2-weighted images (T2WI) (A) and fluid-attenuated inversion recovery (FLAIR) images (B). Diffusion-weighted images (DWI) show weak hyperintense signals in the bilateral thalami (C). Marked hyperintense signals on diffusion-weighted imaging with a dark appearance on apparent diffusion coefficient mapping (D) indicating cytotoxic edema comprise only a portion of the hyperintense lesions on T2WI and FLAIR images of the bilateral thalami. The lesions are accompanied by hypointense lesions on T2* imaging (E). A sagittal section of enhanced CT shows no filling defects in the proximal straight sinus (F).

The marked hyperintense lesions observed on T2-weighted and FLAIR images in both thalami of our patient are striking findings. Approximately 50% of all patients with HE demonstrate normal findings on brain computed tomography and MRI, whereas the remainder exhibit nonspecific findings (8). Various diverse neuroradiological findings have been reported in patients with HE, including brain atrophy (9, 10), white matter abnormalities (2), cortical edema (11) and miscellaneous findings (12, 13). To the best of our knowledge, bilateral thalamic lesions, as shown in this report, have not been described in previous case reports of HE. The pathogenesis of HE remains unclear because precise neuropathological data are lacking; however, the variability in clinical features and radiological findings suggests that HE may have a variety of causes. One possible pathologic mechanism of HE is the involvement of an autoimmune inflammatory process because pathological findings of brain biopsy specimens have revealed marked lymphocytic infiltration of parenchymal arterioles and venules (3). Furthermore, in one patient with HE, the autopsy findings demonstrated lymphocytic infiltration throughout the walls

of arterioles and venules in the brain stem, white matter, cortex and leptomeninges (4).

The MRI findings in our patient represented possible vasogenic edema in the bilateral thalami, which appeared as a weakly hyperintense signal on DWI. A markedly hyperintense signal on DWI with a dark appearance on ADC mapping indicated cytotoxic edema, which comprised only a portion of the hyperintense lesions on FLAIR images of the bilateral thalami. These radiological findings suggested the coexistence of vasogenic and cytotoxic edema in the bilateral thalami in our patient. Grommes et al. reported that hyperintensity on DWI associated with abnormal signal intensity on ADC mapping, as found in our patient, indicates an acute vascular pathological process in HE patients (14). These DWI changes reportedly also occur in patients with central nervous system vasculitis (15). In addition, the presence of anti-NAE antibodies in the serum suggested autoimmune vasculitis as a cause of our patient's findings because NAE is abundantly expressed in vascular endothelial cells and is associated with other vasculitic diseases such as Kawasaki disease (16). Our patient's clinical features and

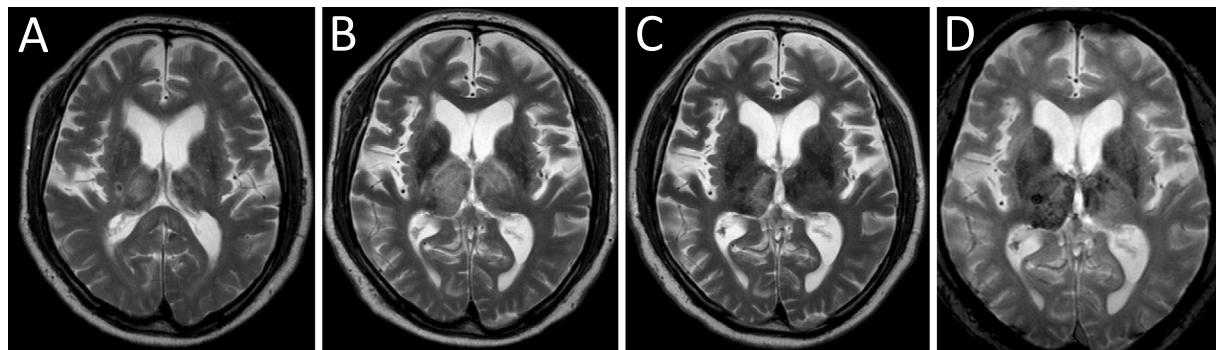


Figure 2. Time course of the thalamic lesions observed on brain MRI. The bilateral thalamic lesions on axial T2WI improved after initial high-dose corticosteroid therapy (A); however, the patient's symptoms later worsened and marked hyperintense lesions reappeared on T2WI in both thalami two weeks after initial treatment (B). Following repeated high-dose corticosteroid treatment, the lesions again improved three months after admission (C); however, multiple hypointense lesions became increased in both thalami on axial T2* imaging (D).

MRI findings suggest that treatment with antiplatelet or anti-coagulant medications can exacerbate secondary hemorrhagic changes in HE patients with anti-NAE antibodies.

Moreover, the location of the brain lesions in our patient is a matter of debate. Evidence shows that patients with end-stage renal disease exhibit endothelial dysfunction. Because sympathetic innervation of the vertebrobasilar circulation is relatively sparse, it is possible that blood-brain barrier disruption predominantly develops in the posterior circulation in patients with renal disease. Dhillon et al. recently reviewed the clinical features of posterior reversible encephalopathy syndrome in patients with autoimmune disease (17). Notably, 38 of 48 patients with autoimmune disease had systemic lupus erythematosus and most also had renal disease. In our opinion, the combined impact of autoimmune disease and renal disease may be linked to the development of bilateral and symmetrical lesions of the thalami.

In conclusion, we herein reported a case of HE with marked bilateral thalamic lesions on MRI. Although the precise cause of HE remains unclear, an acute vascular pathologic process is likely. Physicians should include HE as a differential diagnosis in patients with subacute onset of cognitive impairment. Furthermore, antiplatelet and anticoagulant therapy may exacerbate secondary hemorrhagic changes associated with encephalopathy in patients with anti-NAE antibodies, the presence of which is suggestive of an underlying vascular pathology.

The authors state that they have no Conflict of Interest (COI).

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