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Case Report

Myelitis preceding anti-N-terminal of α-enolase antibody-positive Hashimoto's encephalopathy ☆

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ABSTRACT

Hashimoto's encephalopathy is an autoimmune disease characterized by diverse clinical and imaging manifestations, often presenting considerable challenges in its diagnosis, especially when myelitis occurs before the onset of encephalopathy. Anti-N-terminal of α-enolase antibodies targeting the N-terminal of α-enolase are specific serum markers of Hashimoto's encephalopathy; however, studies analyzing their association with myelitis are lacking. Herein, we describe the case of a patient with myelitis who later developed encephalopathy. Owing to positivity for anti-N-terminal of α-enolase antibodies in the serum, a diagnosis of Hashimoto's encephalopathy was made. Detecting anti-NAE antibodies can be useful in diagnosing myelitis of unknown etiology.

Introduction

Hashimoto's encephalopathy, a rare autoimmune encephalopathy, was first described in 1966 by Brain et al. [1,2]. The estimated prevalence of Hashimoto's encephalopathy is approximately 2.1 per 100,000 individuals annually [3]. Diagnosing this condition remains challenging owing to its diverse clinical and radiological manifestations. However, the identification of anti-N-terminal of α-enolase (NAE) antibodies targeting the N-terminal of α-enolase in serum provides valuable diagnostic information [4–6]. The specificity of anti-NAE antibodies for Hashimoto's encephalopathy is 90%, which is considered high [7]. Although spinal cord involvement related to Hashimoto's disease has been previously reported [8,9], spinal cord involvement with serum positivity for anti-NAE antibodies has not been documented to date. Pyramidal tract symptoms are frequently observed in Hashimoto's encephalopathy, but abnormalities in the pyramidal tracts on magnetic resonance imaging (MRI) are not consistently reported [10]. Herein, we report a case of Hashimoto's encephalopathy involving the right pyramidal tract with an initial onset of myelitis that was positive for anti-NAE antibody.

Case presentation

A 70-year-old man presented with complaints of numbness of the lower limbs and urinary retention. The laboratory investigations indicated a normal leukocyte count (7390/μL),

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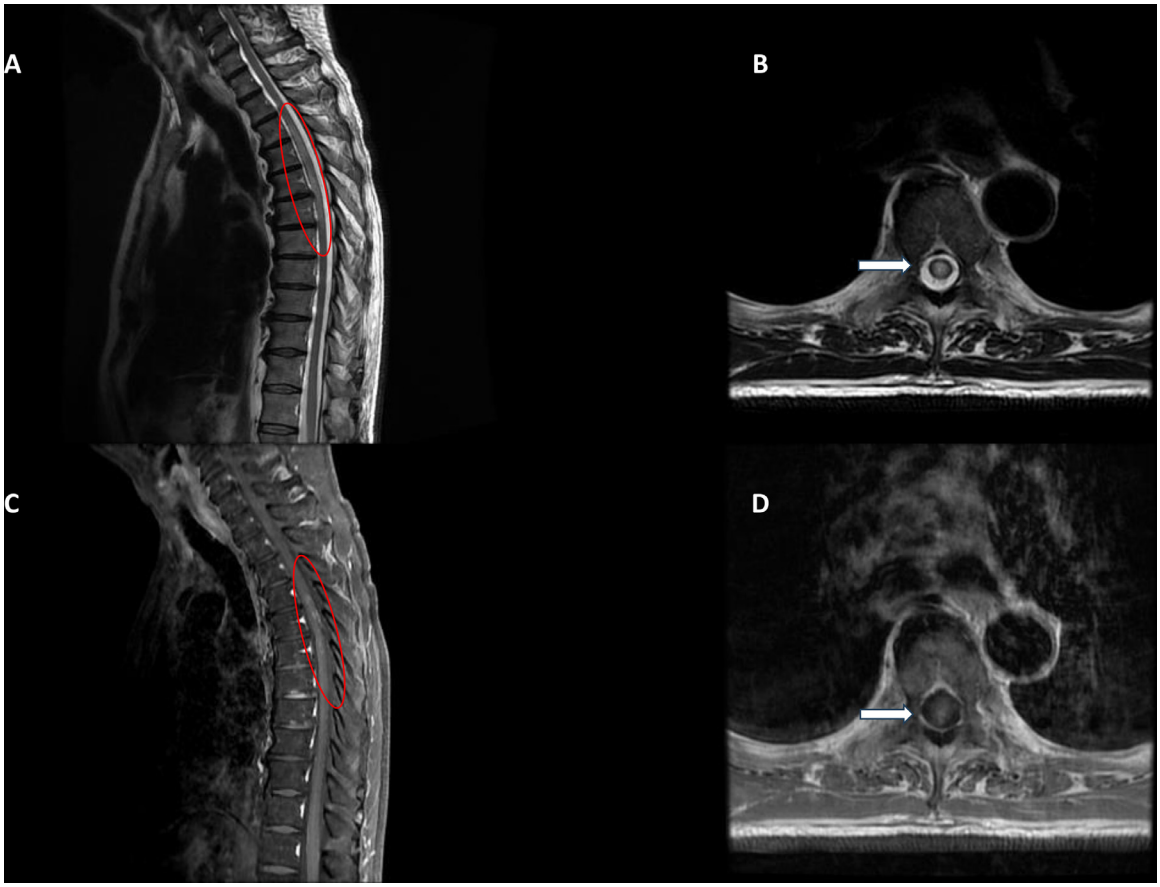

Fig. 1 – Hyperintense lesions in the thoracic spinal cord from the Th4 to Th8 levels (red circle) (A, B). Contrast enhancement was observed within these lesions (arrow) on post-contrast T1-weighted imaging (T1-WI) (C, D).

platelet count (349,000/μL), blood glucose level (88 mg/dL), and a slightly reduced hemoglobin concentration (11.4 g/dL). No abnormalities were detected in the liver or kidney function tests or the serum electrolytes. Thyroid function tests were normal, with free T3 at 2.04 pg/mL and free T4 at 1.16 ng/mL. However, anti-thyroid peroxidase (TPOAb) antibodies were detected. Further screening tests for anti-nuclear antibodies, rheumatoid factor, anti-ds-DNA, anti-RNP, anti-Sm, anti-SS-A, anti-SS-B, anti-aquaporin 4, anti-GQ1b, anti-GM1, anti-LGI1, anti-CASPR2, anti-MOG, anti AQP4, and anti-GFAP antibodies yielded negative results. The oligoclonal bands PR3-ANCA and MPO-ANCA were also negative. Blood cultures revealed no bacteria. Tests for tuberculosis, herpes simplex virus, varicella-zoster virus, cytomegalovirus, and elevated β-D-glucan were all negative in both blood and CSF, making infectious disease diagnosis less likely. Neoplasia markers, including test results for soluble IL-2 receptor, were negative, while a CT scan of the trunk revealed no tumors throughout the body. Conversely, cerebrospinal fluid analysis demonstrated an elevated cell count (29/μL) and protein concentration (300 mg/dL) without a substantial reduction in glucose concentration. MRI of the thoracic spine (Fig. 1) revealed T2-weighted hyperintense lesions extending from the Th4 to Th8 levels, with contrast enhancement observed within these lesions. While the etiology of the spinal cord lesions could not be identified at that point, the patient was treated with steroid pulse therapy for immune-mediated myelitis after ruling out an infection. The patient was discharged following improvement in symptoms and imaging findings. After discharge, considering the positive TPOAb and the robust positivity of anti-NAE antibodies specific for Hashimoto's encephalopathy measured during hospitalization, myelitis was speculated to be related to Hashimoto's autoimmune disease. The good response to steroid treatment and positive results for TPOAb and anti-NAE antibodies agreed with a diagnosis of Hashimoto-related myelopathy, although brain MRI showed no abnormalities at that point.

No particular problems occurred after discharge, and steroid treatment gradually tapered. However, after 2 years, the patient presented to the emergency department with complaints of posterior neck pain and fever, with worsening consciousness. Paralysis of the left upper and lower extremities with signs of meningeal irritation was observed during the clinical examination. No complaints of nausea, stuttering, vision loss, or visual field defects were reported. Diffusion-weighted brain MRI imaging (Fig. 2) revealed a hyperintense lesion of the right pyramidal tract, characterized by reduced apparent diffusion coefficient values. Punctate areas of contrast enhancement were visible within the lesion. Diffusion restriction was also observed in the genus of the corpus callosum. Hyperintense signals on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences were evident in the thala-

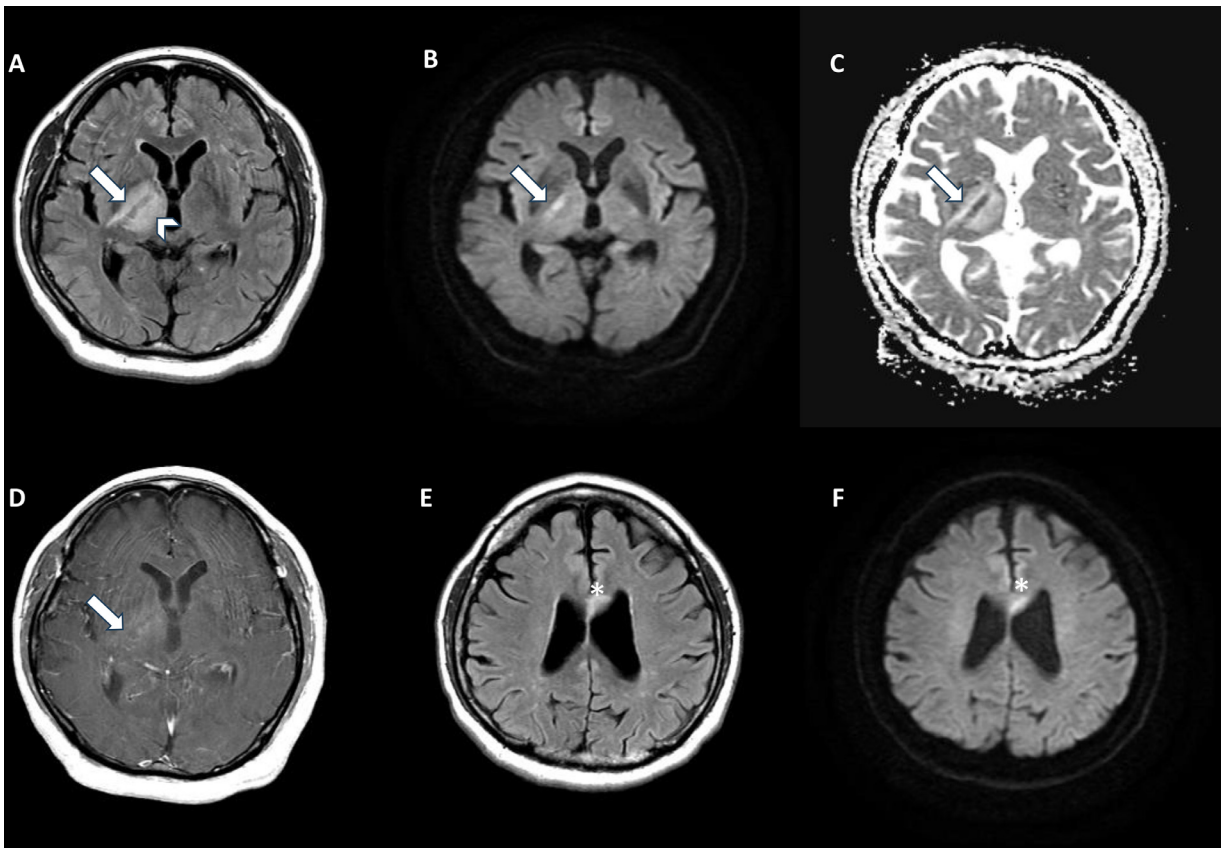

Fig. 2 – High signal intensity lesion in the right pyramidal tract (arrows) on fluid-attenuated inversion recovery (FLAIR) (A) Diffusion-weighted image (DWI) (B) and apparent diffusion coefficient (C) showing diffusion restriction in the lesion (arrows). Patchy contrast effect observed around the pyramidal tract (arrows) on post-contrast T1-WI (D). FLAIR image in the same level showing high signal intensity in the right thalamus (arrowhead), with no obvious contrast effect on post-contrast T1 images or diffusion limitation on DWI. Hyper signal was observed in the left genu of corpus callosum (*) on DWI (E) and FLAIR (F).

mus and right pyramidal tract, with no evidence of periventricular abnormalities, such as the lesions in the midbrain aqueduct or optic nerve (not shown).

Additionally, no notable abnormalities were detected on computed tomography of the neck, including the thyroid and trunk (data not shown). Additionally, anti-AQP-4 antibodies were not detected, thereby ruling out the possibility of neuromyelitis optical spectrum disorders (NMOSD) [11]. Other antibodies related to autoimmune encephalopathy, such as those for MOGAD and paraneoplastic syndrome, were also not detected. TPOAb and anti-NAE antibodies were again positive. Therefore, based on the pertinent clinical history, including during steroid tapering and laboratory findings indicative of other causative diseases, a conclusive diagnosis of Hashimoto's encephalopathy was established. steroid pulse therapy was initiated, which led to an improvement in clinical symptoms, and the patient was discharged.

Discussion

Hashimoto's encephalopathy, an autoimmune-mediated encephalitis, has a prevalence of 2.1/100,000 among adults in Europe and the United States [3]. The disease is primarily idiopathic in origin, and the underlying pathogenesis remains unknown. Despite the scarcity of reports on brain pathology, instances of lymphocytic infiltration around small veins and arterioles, which are indicative of vasculitis, have been documented in both brain biopsies and autopsies [12,13]. Conversely, cerebral parenchymal inflammation devoid of vasculitis, characterized by inflammatory cell infiltration and gliosis within the cerebral parenchyma, has been observed [14]. The exact immunological target in HE remains to be fully elucidated; therefore, understanding whether the autoimmune response primarily targets the vascular system or neuronal cells warrants further investigation.

Despite a reported thyroidal association, approximately 50% of patients with Hashimoto's encephalopathy demonstrate normal thyroid function, albeit with serum positivity for TgAb and TPOAb [15]. Although thyroid function was normal in our patient, the presence of TPOAb and anti-NAE antibodies, which are specific to Hashimoto's encephalopathy led to this diagnosis. Therefore, normal thyroid function does not rule out the possibility of Hashimoto's encephalopathy.

The clinical manifestations of Hashimoto's encephalopathy are categorized into three primary types: an acute encephalopathy type characterized by acute consciousness

disturbance and psychiatric symptoms, a psychotic type manifesting with chronic depressive and schizophrenia-like symptoms, and a slowly progressive type exhibiting cerebellar ataxia [16]. Cognitive dysfunction and seizures are relatively common neurological manifestations, often accompanied by pyramidal tract disorders [17]. Our patient presented with cognitive dysfunction and pyramidal tract disorder; a relatively typical clinical presentation of Hashimoto's encephalopathy.

Hashimoto's encephalopathy manifests diverse radiological findings, of which a white matter encephalopathy-like presentation with nonspecific T2-weighted and FLAIR hyperintensities located in the deep white matter of the cerebrum is a characteristic finding [18]. This specific finding is common among young and middle-aged women. Other reported cases demonstrated image findings resembling limbic encephalitis [19], Creutzfeldt-Jakob disease [20], cerebellar atrophy [21], and mass-like lesions [22]. Single photon emission computed tomography (SPECT) may be a useful modality for diagnosing Hashimoto's encephalopathy when the MRI findings are inconclusive. SPECT imaging may reveal hypoperfusion in regions integral to memory and mental function, including the left prefrontal cortex, medial prefrontal cortex, and anterior cingulate gyrus [10,23].

To our knowledge, this is the first report of a case of myelitis in which the patient tested positive for anti-NAE antibodies. In the present case, the diagnosis was challenging because myelitis preceded Hashimoto's encephalopathy. Owing to the presence of a large spinal cord lesion, NMOSD, anti-MOG antibody-related disease, and autoimmune glial fibrillary acidic protein astrocytopathy were suspected; however, all associated antibodies were negative. Upon recurrence, the patient's medical history indicated negative results for infectious tests and the absence of antibodies such as anti-AQP4. No other causative disease other than Hashimoto's encephalopathy could explain the pathological process in the second episode. This supports the hypothesis that both myelitis and Hashimoto's encephalopathy represent a unified, continuous autoimmune process. Although rare, myelitis associated with Hashimoto's disease has been previously reported. A study on the etiology of acute myelitis, including 96 patients, reported Hashimoto's disease in one patient [9]. Additionally, 2 of 55 patients with chronic myelitis had Hashimoto's disease. Myelitis due to Hashimoto's disease that occurred 2 months before the onset of Hashimoto's encephalopathy was reported in 1 patient [8]. In both patients, the presence of anti-TPO antibodies was indicative of Hashimoto's disease. Considering that Hashimoto's encephalopathy is not commonly associated with myelitis, anti-NAE antibodies are not typically examined in myelitis. However, the cause of myelitis is unknown in 30% of patients [24]. Therefore, myelitis associated with anti-NAE antibodies may have been overlooked. It is common to find positive thyroid antibodies in cases of transverse myelitis [25].

The "molecular mimicry" of epitopes between thyroglobulin and myelin should be considered [26]. Thyroid peroxidase antibodies(ATAs) can produce inflammatory immune complexes and modulate immune responses to myelin basic protein [27,28]. Moreover, Ota [28] reported high titers of anti-thyroglobulin antibodies regarding AQP4 antibody-negative transverse myelitis, suggesting the presence of additional target antigens other than AQP4 in thyroid tissues [28]. Considering these findings, we propose the hypothesis that myelitis can precede Hashimoto's encephalopathy.

In the present case, the lesion was longer than three vertebrae; however, spinal-cord lesions associated with Hashimoto's disease have been reported in both long-cord [9] and short-cord lesions [8], indicating that myelitis associated with Hashimoto's disease can cause both long- and short-segment lesions. The relationship between the length of spinal lesions and anti-thyroid antibodies remains uncertain, warranting further study [25]. However, a recent study noted that TPOAb was associated with longitudinally extensive transverse myelitis (LETM), responded well to steroids, and required long-term immune- suppression [29]. Therefore, while the evidence is not robust, this supports the hypothesis that lesion length could serve as an indicator of Hashimoto's myelitis.

While Hashimoto's encephalopathy presenting with pyramidal tract symptoms is common, abnormal MRI signals in the pyramidal tracts have been rarely documented. Dihné et al. reported the case of a 61-year-old man with progressive cognitive dysfunction and tremor, with high signal areas on FLAIR images in the bilateral pyramidal tracts and the bilateral frontal and temporal lobes [10]. Steroid pulse therapy demonstrated effectiveness, resulting in near-complete resolution of both clinical and imaging abnormalities. Abnormal MRI signals in the pyramidal tract are typical manifestations of Hashimoto's encephalopathy in patients with apparent clinical symptoms.

While NMOSD is the prevalent autoimmune encephalopathy with pyramidal tract involvement [30], Hashimoto's encephalopathy should also be considered based on imaging findings. Notably, myelitis may occur in Hashimoto's disease and may precede Hashimoto's encephalopathy. Identifying myelitis of otherwise unknown origin and the detection of anti-NAE antibodies may be significant in the diagnosis.

Conclusion

We reported a case of Hashimoto's encephalopathy with abnormal signals along the spinal cord and right pyramidal tract. The possibility of Hashimoto's encephalopathy in patients presenting with a wide spectrum of neurological symptoms and abnormal imaging findings should be considered. To date, this is the first study to report a case of anti-NAE antibody-positive myelitis. Although spinal cord lesions associated with Hashimoto's disease are rare, identifying anti-NAE antibodies are imperative to rule out myelitis of unknown cause.

Patient consent

Informed consent was obtained from the patient.

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