CASE REPORT

Hashimoto’s Encephalopathy Presenting with Smoldering Limbic Encephalitis

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Abstract:
Hashimoto’s encephalopathy (HE) is a steroid-responsive autoimmune encephalopathy associated with Hashimoto thyroiditis. We herein report a case of HE manifesting “smoldering” limbic encephalitis with persisting symptoms and abnormalities on examinations. Although our patient experienced partial clinical remission after treatment, hippocampal hypermetabolism on [¹⁸F] fluorodeoxyglucose positron emission tomography (FDG-PET) and subclinical seizures on video electroencephalography persisted. Hypermetabolism on FDG-PET was improved by additional prednisolone therapy. Thus, as with other autoimmune limbic encephalitis cases, HE can take a course of “smoldering” encephalitis. FDG-PET and electroencephalogram findings can reflect the disease activity degree in such patients, although with certain neurophysiological and biochemical distinctions.

Key words: Hashimoto’s encephalopathy, FDG-PET, video EEG, autoimmune limbic encephalitis, anti-NAE antibody

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Introduction

Hashimoto’s encephalopathy (HE) is an encephalopathy related to thyroid autoimmunity and was first described by Brain et al. (1). HE has various clinical characteristics, but the precise pathomechanism has not been elucidated (2). Although HE is a relatively rare disease, it is sometimes misdiagnosed as other neurological disorders, such as Alzheimer’s disease, schizophrenia, and depression, or goes undiagnosed, due to its various manifestations (3-6). Yoneda et al. revealed that serum anti-NH2 terminal of α-enolase (NAE) antibody was a specific biomarker of HE and that a subtype of HE sometimes showed limbic encephalitis, namely anti-NAE antibody limbic encephalitis (7, 8). We previously reported a case of anti-leucine-rich glioma inactivated 1 protein (LGI1) antibody encephalitis in which hypermetabolism on [¹⁸F] fluorodeoxyglucose positron emission tomography (FDG-PET) and subclinical seizure patterns on video electroencephalogram (vEEG) chronically persisted, leading us to term the disorder “smoldering” encephalitis (9, 10). In autoimmune encephalitis, hypermetabolism on FDG-PET has generally been considered to reflect the degree of inflammation, which can be a surrogate marker for its treatment (11-15).

We herein report a case of HE presenting with “smoldering” limbic encephalitis. Both FDG-PET and long-term vEEG were useful for evaluating the disease activity.

Case Report

A 68-year-old Japanese woman without a remarkable medical history developed a 1-week history of memory impairment, resulting in some trouble at her workplace. She appeared mostly normal, but her activities of daily living, such as cooking, were slightly impaired. She became confused after a few days and then developed somnolence, at which point she was admitted to a hospital.

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A neurological examination revealed severe consciousness disturbance that precluded the Mini-Mental State Examination (MMSE) evaluation. The findings of a general blood examination were within normal limits. Thyroid-stimulating hormone (TSH), free thyroxine (T4) and free triiodothyronine (T3) were almost within normal limits (0.57 μIU/mL; normal 0.34-3.88 μIU/mL, and 1.2 ng/dL; normal 0.8-1.8 ng/dL, 2.0 pg/dL; normal 2.1-4.0 pg/mL, respectively). A cerebrospinal fluid (CSF) analysis showed mildly elevated protein (44 mg/dL) and lymphocyte dominant pleocytosis (24 cells/mm³, 96% monocytes). Brain magnetic resonance imaging (MRI) showed bilateral high-intensity lesions in the hippocampus and amygdala on fluid-attenuated inversion recovery (FLAIR) imaging (Fig. 1A). Whole-body contrast-enhanced computed tomography (CT) showed no mass lesion indicating a suspected malignant tumor. An electroencephalogram (EEG) showed spike and wave complexes and periodic discharge patterns in the bilateral temporal areas. The patient was discharged 2 months after the onset of initial symptoms with an MMSE score of 28/30.

Figure 1.  Chronological changes in brain MRI. (A) At the initial attack, brain magnetic resonance imaging (MRI) on fluid-attenuated inversion recovery (FLAIR) showed enlargement of bilateral medial temporal lobes with high-intensity signals. (B) At the second attack, MRI showed hyperintense lesions in the bilateral medial temporal lobe with slight atrophy. (C) Seven months after the onset, MRI showed bilateral hippocampal atrophy with high-intensity signals. (D) Twelve months after the onset, MRI showed no remarkable interval changes from (C).

Two months later, she gradually developed fatigue, daytime sleepiness, and exacerbation of memory impairment. A physical examination showed both consciousness and cognitive impairment with an MMSE score of 25/30. Brain MRI showed bilateral hippocampal high-intensity lesions (Fig. 1B), but an EEG showed no epileptiform discharges. She was diagnosed with a relapse of HE, as IVMP and oral GCS dramatically improved her symptoms. We continued levetiracetam because the EEG showed epileptiform discharges in the bilateral temporal areas. The patient was discharged 2 months after the onset of initial symptoms with an MMSE score of 28/30.

Three months later, she was admitted to the hospital for a further evaluation since her memory impairment had remained without improvement. A neurological examination revealed mild memory impairment on the MMSE (score of 27/30) and the Wechsler Memory Scale-Revised (WMS-R) (verbal memory: 66, visual memory: 88, general memory: 70, attention: 101, and delayed memory: <50). A laboratory examination was normal except for positive findings for anti-TPO antibody (37.9 IU/mL), while all other serological tests, including anti-thyroglobulin antibody (<10.0 IU/mL; normal <28.0 IU/mL), were negative. A CSF examination revealed a mild elevation in protein (56.6 mg/dL, >11 cells/mm³, IgG index 0.47), while bacterial culture and cytology...
of the CSF were negative. Brain MRI on FLAIR imaging showed bilateral hippocampal high intensity lesions and atrophy (Fig. 1C). FDG-PET showed hypermetabolism in the left posterior hippocampus (Fig. 2A). In order to evaluate the degree of hypermetabolism on FDG-PET suggesting inflammation objectively and chronologically, we measured the standardized uptake value (SUV) of the region of interest (ROI) including the highest SUV value.

We introduced IVMP at 1,000 mg/day for 3 consecutive days followed by oral GCS at 25 mg/day. FDG-PET after additional IVMP treatment showed remarkable improvement of hypermetabolism of the left hippocampus (Fig. 2B). We measured the SUV on FDG-PET, including the maximum SUV value with the same-size ROI as at the initial measurement. The mean SUV was 4.38, and the maximum SUV was 4.96, suggesting an improvement in hypermetabolism compared with that before additional IVMP therapy, although the patient’s memory impairment was unchanged.

One month later, her serum tested positive for anti-NAE antibody, with negative findings for anti-voltage-gated potassium channel-complex (VGKC-complex) autoantibody, including anti-LGI1 antibody and anti-contactin-associated protein 2 (CAPSR-2) antibody; anti-glutamate receptor ε2, ζ1, and δ2 antibody; anti-Ma1 antibody; anti-Ma2 antibody; anti-amphiphysin antibody; anti-CV2/collapsing response mediator protein 5 (CRMP5) antibody; anti-Ri antibody; anti-Yo antibody; and anti-HuD antibody. We did not measure anti-gamma-aminobutyric acid (GABA)-A/B receptor antibodies. TSH, fT4, and fT3 were all within normal limits (1.52 μIU/mL, 1.21 ng/dL, and 3.2 pg/dL, respectively). The dosage of oral GCS was gradually reduced.

Six months later, she was admitted to the hospital again for a re-evaluation at 9 mg/day of oral GCS. Her mild cognitive impairment remained unimproved on the MMSE (25/30) and WMS-R (verbal memory: 67, visual memory: 82, general memory: 69, attention: 120, and delayed memory: <50). Brain MRI showed no remarkable change in the interval from the previous examination (Fig. 1D), and FDG-PET revealed that the improvement in the hypermetabolism in the left posterior hippocampus had been maintained as well (Fig. 2C). We measured the SUV of FDG-PET and also analyzed the findings of previous FDG-PET examinations. The mean SUV was 4.38, and the maximum SUV was 5.04, indicating that the degree of hypermetabolism was almost the same as that just after the additional IVMP therapy. An overnight long-term vEEG revealed two subclinical seizures arising from the right mid-posterior temporal area and six from the left temporal area (Fig. 3).

Given the symptoms and examination results, we considered the degree of “smoldering” to be almost the same as it had been six months earlier. At present, the disease is well controlled with oral GCS at 9 mg/day without further relapse.

### Discussion

The patient developed HE manifesting as limbic encepha-

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**Figure 2. Sequential changes on fluorodeoxyglucose-positron emission tomography (FDG-PET).**

Fluorodeoxyglucose-positron emission tomography (FDG-PET) showing hypermetabolism in a left posterior hippocampal lesion [standardized uptake value (SUV): mean 6.26, max 7.29] (A), which improved after steroid treatment (SUV: mean 4.38, max 4.96) (B). Image showing that, five months after the initiation of steroid therapy, the improvement in the hypermetabolism had been maintained (SUV: mean 4.38, max 5.04) (C). The SUV values were measured in the region of interest (ROI) including the highest SUV value.
lipitis with persisting chronic symptoms and abnormalities in laboratory, neurological, imaging, and EEG examinations, suggesting a “smoldering” pathophysiology. This case raises two important new clinical considerations: 1) HE can present as “smoldering” limbic encephalitis, and 2) FDG-PET and EEG can reflect the disease activity on HE presenting as limbic encephalitis as previously reported in patients with other types of autoimmune limbic encephalitis (9, 10).

HE was first reported by Brain et al. in 1966, and about 300 cases have been reported subsequently (1, 2). For its diagnosis, anti-TPO antibody and the exclusion of other forms of encephalitis are essential (16, 17). Based on its clinical course, HE is classified into acute and diffuse types. The diffuse type often manifests as progressive dementia (18). In some previous cases of HE, the late initiation of treatment was considered to increase the risk of residual memory impairment and/or hippocampal atrophy (5, 19). In 2002, Yoneda et al. found anti-NAE antibody to be a specific antibody of HE (7). Furthermore, in 2017, they reported a subtype of HE presenting as limbic encephalitis (8). Based on their findings, the case reported herein should be included in this subtype of HE because of the observations of bilateral high-intensity lesions in the mesial temporal lobes on brain MRI and the presence of symptoms associated with dysfunction of the limbic system, such as memory impairment and consciousness disturbance.

Anti-LGI1 antibody limbic encephalitis is often followed by a mild but long-lasting residual functional disorder, probably due to inflammation (20). Indeed, ongoing functional complications were observed in two cases of “smoldering” anti-LGI1 antibody encephalitis reported by our group (9, 10). Similarly, our case of HE presented with left posterior hippocampal steroid-responsive hypermetabolism on FDG-PET and subclinical seizures on an EEG, both of which seemed to reflect persistent inflammation. Some types of autoimmune encephalitis emerge as severe refractory status epilepticus, such as new-onset refractory status epilepsy (NORSE), which shows refractory clinical seizures (21). Compared with the severe encephalitis that is refractory and usually causes a decline in activities of daily living, our concept of “smoldering encephalitis” at this point is different in that it causes mild or no clinical seizures and very gradual or no higher brain and/or cognitive dysfunction. Patients with “smoldering encephalitis” present with “smoldering” inflammation, as suggested by subclinical seizure patterns and epileptiform discharges on EEGs and hypermetabolism on FDG-PET. We therefore considered the clinical course of the present HE patient to be “smoldering” encephalitis with hippocampal atrophy, which is often seen in cases of anti-LGI1 antibody encephalitis.

Recently, the clinical importance of FDG-PET in autoimmune encephalitis, including anti-LGI1 antibody encephalitis, has been emphasized (22). Although whether hypermetabolism itself is due to inflammation or epileptic activity is

Figure 3. Subclinical seizures on an overnight video-electroencephalogram (vEEG). An overnight vEEG performed 1 year after the clinical onset showing subclinical seizure patterns both in the left temporal area (6 times in 24 hours) and right temporal area (2 times in 24 hours). A representative subclinical seizure pattern arising from the left temporal area is presented (red dotted lines). LFF: low-frequency filter, HFF: high-frequency filter.
controversial, FDG-PET has been considered to be more sensitive than MRI in terms of detecting inflammation (11-15). In HE patients, FDG-PET has been evaluated only in two case reports. One case showed diffuse unilateral temporal hypometabolism and the other medial and superior dorsolateral frontal hypometabolism, and both were responsive to steroids (23, 24). In contrast, our HE patient showed steroid-responsive focal hypermetabolism, suggesting active inflammation with an underlying mechanism of autoimmune abnormalities observable on FDG-PET, although we could not deny the possibility of hypermetabolism due to residual epileptic activity. In addition, the chronological decrease in the SUV values of this lesion may be partially explained by the partial volume effect, considering the small size of the focal lesion presenting with gradual atrophy. The differences between the present and previous cases might be due to the varied clinical characteristics of HE; our case showed limbic encephalitis, while most cases of HE present with cortical and/or subcortical dysfunction. In “smoldering” limbic encephalitis of HE, hypermetabolism on FDG-PET may reflect the disease activity.

Improving the frequent seizure patterns on EEG commonly seen in anti-LGI1 antibody encephalitis is thought to be important for resolving memory impairment (9, 25, 26). Thus, treating subclinical seizures in autoimmune encephalitis may contribute to long-term memory improvement. HE generally presents with various EEG abnormalities, such as generalized slow waves, lateralized periodic discharges, triphasic waves, and temporal epileptiform activities (18, 27-30). Clinical symptoms and slow waves on EEG generally have been considered to correlate with the disease activity in conventional types of HE (31). In contrast, the correlation between the epileptiform discharges and disease severity in HE is still unclear. As in our case, despite improvements on FDG-PET, the re-evaluation of the long-term vEEG showed no obvious improvement with regard to the seizures with chronic lateralizing variation. Given that the EEG seizure patterns persisted while hypermetabolism on FDG-PET was relatively improved, it is uncertain whether the residual memory impairment in this particular HE patient was due to the sequelae of encephalitis or to “smoldering” of encephalitis. The long-term follow-up of this patient will help clarify this issue.

In previous cases of anti-LGI1 antibody encephalitis, early intensive treatment correlating with decrements in the titer of the antibody resulted in a good prognosis, but the optimal treatment regimen and period have not been defined (32). In both anti-LGI1 antibody encephalitis and HE, the diagnosis should be made early and appropriate treatment introduced in order to prevent persistent memory impairment as sequelae, as a delayed diagnosis and treatment are common risk factors for a poor functional outcome (5, 19, 32). The hypermetabolism on FDG-PET in our HE case presenting with “smoldering” limbic encephalitis might have been correlated with the disease activity. Treatments targeting hypermetabolism on FDG-PET might lead to a good memory prognosis in not only anti-LGI1 antibody encephalitis but also “smoldering” limbic encephalitis of HE. Anti-LGI1 antibody encephalitis and HE presenting with limbic encephalitis share some characteristics in that they are both steroid-responsive with little association with tumors, although HE presenting with limbic encephalitis tends to show female predominance and more CSF abnormalities than anti-LGI1 antibody encephalitis (8, 33). LGI1 is the neural membrane protein in the VGKC complex, and its dysfunction has been estimated to lead to neural activity impairment (10). NAE is a protein identified by a proteome analysis using the serum of HE patients, and its pathophysiological role in HE remains unclear (7). Further investigations will be needed to clarify the patho-mechanistic similarities between these two types of limbic encephalitis.

Thus, the accumulation of further cases is needed in order to assess the capability of FDG-PET and long-term vEEG as surrogate markers of disease activity in “smoldering,” autoimmune limbic encephalitis of HE.

Author’s disclosure of potential Conflicts of Interest (COI).

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