Clinical Case Report

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# Multiple intracranial lesions as the unusual imaging features of Hashimoto's encephalopathy

## A case report

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**Abstract**

**Rationale:** Hashimoto's encephalopathy (HE) is associated with autoimmune thyroid disease and is complex, diverse, and easily misdiagnosed. However, if HE is diagnosed and treated in a timely manner, an optimal prognosis may be achieved.

**Patient concerns:** We presented a case of a 63-year-old female patient with paroxysmal dizziness, unsteady gait, emotion apathy, progressive cognitive impairment, and unusual magnetic resonance imaging (MRI) findings.

**Diagnoses:** After suffering for almost 8 years, the patient was diagnosed with HE based on clinical manifestation, abnormal electroencephalogram, unusual MRI findings, sensitivity to cortisol treatment, and characteristic high antithyroid peroxidase antibody (TpoAb) titer.

**Interventions:** The patient continued regular glucocorticoids therapy after intravenous methylprednisolone pulse therapy, neurotrophic drugs, traditional Chinese medicine and rehabilitation to relieve hypermyotonia and cognitive impairment.

**Outcomes:** After combined treatment, the patient's symptoms, electroencephalogram (EEG), MRI, and the TpoAb titer gradually improved. However, the patient had to stop glucocorticoids treatment because of severe osteoporosis, fractures and other adverse reactions. Her symptoms fluctuated, and her TpoAb titer increased again.

**Lessons:** HE may cause highly heterogeneous clinical features, particularly MRI findings. Withdrawal of the systematic glucocorticoids treatment can lead to varied outcomes in these patients.

**Abbreviations:** Aβ protein = amyloid beta protein, AD = Alzheimer's disease, ANCA = antineutrophil cytoplasmic antibodies, BAEP = brainstem auditory evoked potential, CAA = cerebral amyloid angiopathy, CAA-I = cerebral amyloid angiopathy-associated inflammation, CRP = C-reactive protein, CSF = cerebrospinal fluid, CSVD = cerebral small vessel disease, CT = computed tomography, EEG = electroencephalogram, EMG = electromyogram, ESR = erythrocyte sedimentation rate, FLAIR = fluid-attenuated inversion recovery, HE = Hashimoto's encephalopathy, IgG = immunoglobulin G, MMSE = Mini-Mental State Examinations, MRA = magnetic resonance angiography, MRI = magnetic resonance imaging, SWI = susceptibility-weighted imaging, T2WI = T2-weighted image, TgAb = antithyroglobulin antibody, TpoAb = antithyroid peroxidase antibody.

**Keywords:** case report, Hashimoto's encephalopathy, multiple intracranial lesions

## 1. Introduction

Hashimoto's encephalopathy (HE) is an uncommon complex syndrome that can be categorized as vasculitic type, which is characterized by multiple stroke-like episodes, or diffuse type, which is characterized by dementia or progressive mental symptoms. Epilepsy, myoclonus, tremor and stupor are also manifestations of HE. The pathological changes identified in HE mainly occurs in the brain parenchyma around the capillaries, arteriovenous system, meningeal vasculature, and particularly veins and are centered around lymphocyte infiltration and myelin sheath and axon damage.[1] This manuscript describes a case of multiple intracranial lesions as the main imaging findings of HE

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**Table 1**

**Electroencephalogram evolution of the case.**

| Diagnosis date | EEG |
|---|---|
| 2015-4 (Fig. 3A and B) | Bilateral occipital region appears symmetrical 10–12 Hz 20–60 μv low in amplitude α rhythm as the basic rhythm, regulation poor, between 14 and 20 Hz 5–30 μv β activity, more scattered and short 5–7 Hz 30 –60 μv ☒ activity right hemisphere all leads more short–long range 4–7 Hz 60–130 μv high amplitude ☒ burst activity. |
| 2015-5 (Fig. 3C and D) | Bilateral occipital region appears symmetrical 8–10 Hz 10–70 μv low in amplitude to α rhythm advantages as the basic rhythm, regulation poor, between 14 and 30 Hz 5–40 μv β activity, paroxysmal tendency. Parietal and temporal areas after persistent 1–3 Hz 10–100 μv relatively low volatility compound in slow activity, a little irregular bilateral asynchronous appear on the right side, mixed with sharper wave, slow wave sharp, spikes, not A typical three-phase wave discharges when spread to other districts. |
| 2015-9 (Fig. 3 E and F) | Bilateral occipital region appears symmetrical 8.5–10 Hz 10–100 μv low high volatility α rhythm as the basic rhythm, regulation, AM poor, between 14 and 20 Hz 5–30 μv β activity, all leads and more sporadic bursts irregular short to long-range high 4–7 Hz 30–320 μv—high amplitude ☒ activities/2.5–3.9 Hz 30–150 μv irregular high amplitude δ wave or activity, the former head common, mixed with sharper waves, sharp slow-wave, three-phase wave discharges. |
| 2016-4 (Fig. 3 G and H) | Head after bilateral 9.5–11 Hz 20–70 μv α rhythm as the basic rhythm, regulation, poor AM right occipital region α activity decreases with lower amplitudes than the left region, a small amount between 14–30 Hz 5–30 μv β activity, all leads and more scattered in the short to long-range burst 1.8–7 Hz 40–150 μv slow activity, high volatility right hemisphere activity slow, slow right temporal area activities 4–6 Hz 70–150 μv ☒ based activities, which form part rhythm right parietal, posterior temporal region activities 1.8–5 Hz 50–110 μv slow polymorphic δ based activities, mixed with sharp wave, sharp wave distribution, was part of three-phase wave changes. |

EEG = electroencephalogram.

and provides insights obtained from recent relevant literature. Specifically, in regards to patient suffering, we evaluated cerebral amyloid angiopathy-associated inflammation (CAA-I) according to imaging findings. Three hypotheses are proposed at the end of this case report that combine the presentations of CAA-I and HE. This case report was approved by the Ethics Committees of Shenzhen Traditional Chinese Medicine Hospital.

## 2. Case report

A 63-year-old female patient indicated that she had experienced periods of fright when she faced unfamiliarity beginning in 2007. Moreover, she reported being tired during daily activities and complained of paroxysmal dizziness without tinnitus and double vision. These symptoms were relieved after several minutes, which confounded the diagnosis. Until 2012, the patient exhibited decline in memory and judgment as well as difficulties performing calculations when purchasing food. In 2013, these symptoms became worse, and she also experienced personality changes, emotional indifference, instability, a slower walking pace, and difficulty in lifting her legs on steps or flat roads when walking forward. In 2014, the condition worsened; walking by herself became constrained, and she had to walk slowly with support. Her activities of daily living simultaneously became more difficult. The patient began to dress more casually and act in a careless manner. She was subsequently diagnosed with leukoaraiosis and was prescribed donepezil in May 2014; however, her symptoms did not improve. Because of these symptoms, the patient sought treatment at our in-patient department in April 2015. She scored 21 on the Mini-Mental State Examination (MMSE). Routine blood, urine and stool analyses, and the blood biochemistry were normal, C-reactive protein (CRP): 17.6 mg/L (0.0–5.0 mg/L); erythrocyte sedimentation rate (ESR): 99.0 mm/h (0.0–5.0 mm/h), antithyroid peroxidase antibody (TpoAb)> 1087.0 IU/mL (0.0–9.0 IU/mL), and antithyroglobulin antibody(TgAb): 37.73 IU/mL (0.00–4.11 IU/mL) (Table 2). A brainstem auditory evoked potential (BAEP), the brainstem plot indicated mild abnormalities in the left periphery and brain conduction; moreover, the volatility of the right-side periphery and midbrain was relatively low. The electroencephalogram (EEG) findings were moderately abnormal (Table 1). The thyroid was assessed via ultrasound and exhibited multiple hypoechoic groups with real echo unevenness, and a nodular goiter was considered. A brain computed tomography (CT) scan (Fig. 1A and B) indicated white matter ischemic changes; multiple lacunar infarctions; symmetrical spots in the bilateral basal ganglia, which indicated calcification; and degeneration. A brain magnetic resonance imaging (MRI) scan (Fig. 2A–D) indicated multiple abnormal parenchymal signals and lacunar infarctions, white matter demyelination, and cerebral atrophy. Magnetic resonance angiography (MRA) of the brain (Fig. 2E) indicated mild cerebral arterial sclerosis. The enhanced MRI (Fig. 2F) showed multiple abnormal parenchymal signals that were similar to the cavernous hemangioma, which could not be identified. Lumbar puncture was performed on April 23rd; the cerebrospinal fluid (CSF) pressure was 250 mm $H_2O$, and routine CSF parameters and biochemistry were both normal. The CSF protein of the immunoglobulin G (IgG) level in the CSF

**Table 2**

**Several important results.**

| Date | MMSE | TgAb, IU/mL (0.00– 4.11 IU/mL) | TpoAb, IU/mL (0.0–9.0 IU/mL) | ESR, mm/h (0.0–15.0 mm/h) | CRP, mg/L (0.0–5.0 mg/L) | CSF IgG, mg/L (10.0–30.0 mg/L) |
|---|---|---|---|---|---|---|
| 2015-4 | 21 | 37.73 | >1087.0 | 99.0 | 17.6 | 37.1 (45.7) |
| 2015-5 | – | 32.35 | 808.1 | – | – | – |
| 2015-9 | 20 | – | 47.1 | 6.0 | 2.8 | – |
| 2016-4 | 22 | 11.69 | 532.4 | 20 | 2.2 | – |
| 2016-5 | – | 10.91 | 562.2 | – | – | – |

CRP = C-reactive protein, CSF = cerebrospinal fluid, ESR = erythrocyte sedimentation rate, MMSE = Mini-Mental State Examinations.

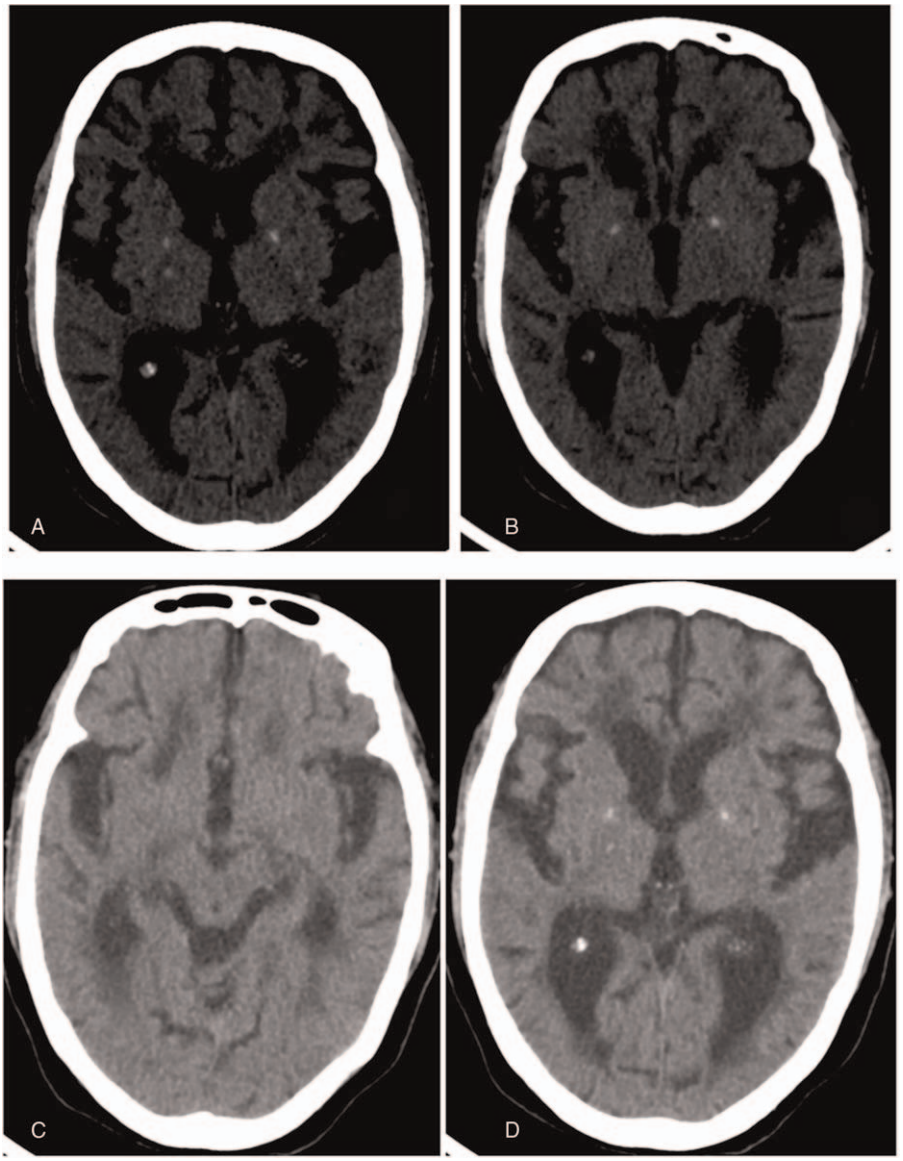


**Figure 1.** April 2015 brain CT scan (A, B): Symmetry visible image density is slightly flaky, and the bilateral basal ganglia and semioval center exhibit multiple punctate low density white matter, bilateral basal ganglia with visible symmetry punctate calcification. September 2015 brain CT scan (C, D): Bilateral symmetry visible ventricle white matter halo density changes and right basal ganglia visible low density strips. CT = computed tomography.

was 37.1 mg/L (10.0–30.0 mg/L) (Table 2). A repeat lumbar puncture on April 30 indicated that the CSF pressure was 180 mm $H_2O$; a re-examination of the routine CSF parameters and biochemistry was normal, the IgG level in the CSF was 45.7 mg/L (Table 2), and no IgG-type oligoclonal band was identified in the CSF or serum. Paraneoplastic syndrome-associated antibodies of the blood and the CSF (anti-Hu antibody IgG, anti-Yo antibody IgG, anti-Ri antibody IgG, anti-Ma2 antibody IgG, anti-Cv2 antibody IgG, and anti-amphiphysin IgG antibodies) were negative; and CSF cytology revealed the presence of small lymphocytes. Summarizing the above clinical evidence indicated that a diagnosis of HE should be considered. Intravenous methylprednisolone pulse therapy was initiated on May 8 2015, which included 500 mg for 3 days, 250 mg for 3 days, and 120 mg for 3 days. The maintenance treatment was consisted of 60 mg of oral prednisone. Antithyroid antibody tests on May 15 revealed 32.35 IU/mL TgAb and 808.1 IU/mL TpoAb (Table 2); moreover, EEG findings were moderately/severely abnormal (Table 1). The cognitive impairment and unsteady gait of the patient slightly improved after the above treatment. The patient continued regular hormone therapy, and the clinical manifestation did not become worse. In September 2015, the patient was hospitalized in our department for referral. Her MMSE score was 20. The ESR and CRP were both normal, and the TpoAb was 47.1 IU/mL (Table 2). The BAEP amplitude was decreased. The EEG was moderately abnormal (but was improved compared with the EEG obtained on May 15, 2015) (Table 1). Brain CT (Fig. 1C and D) indicated that the right basal ganglia lesions had softened, and white matter ischemic changes were evident. Brain MRI (Fig. 2G–K) indicated multiple lacunar infarcts, white matter demyelination and brain atrophy. The presence of multiple punctate low signals in the brain parenchyma suggested that a diagnosis of HE should be considered. We advised the patient to continue oral hormone and other symptomatic treatments, such as neuro-

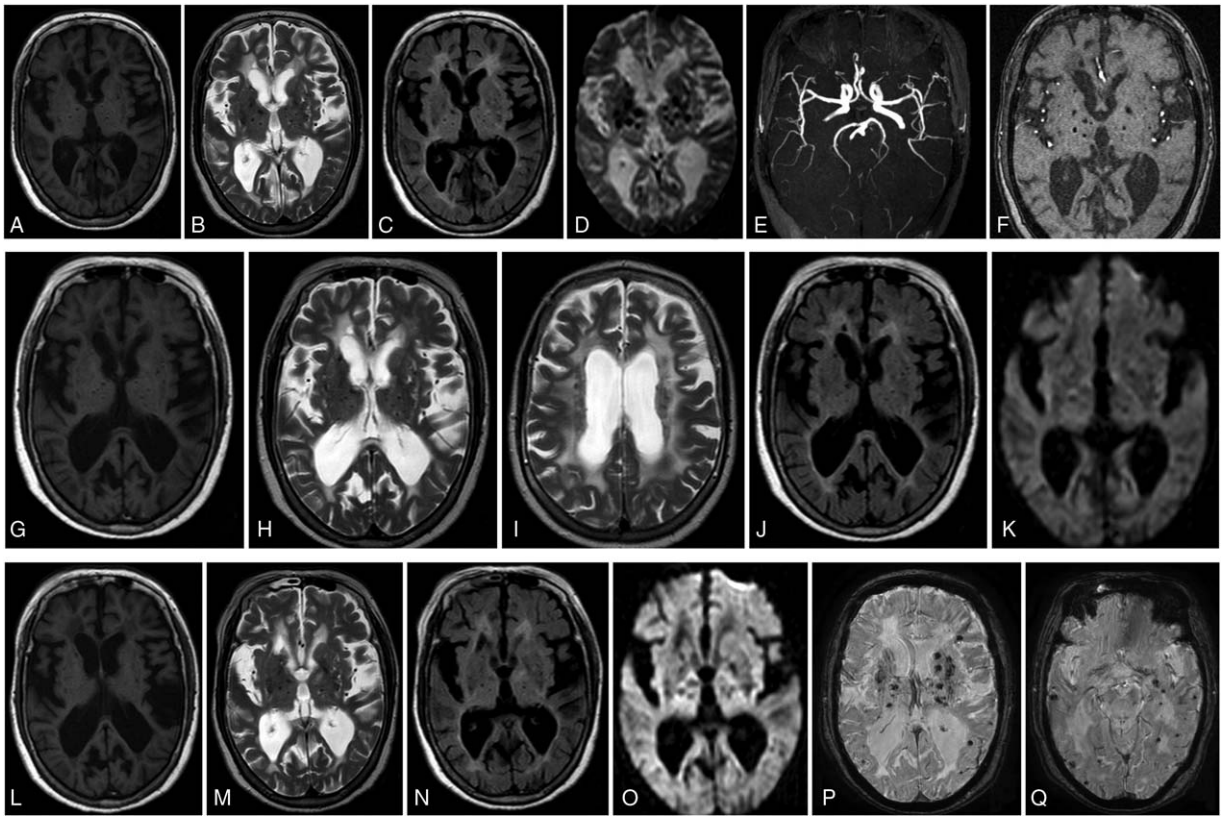


**Figure 2.** Magnetic resonance evolution of the case. Brain MRI of the case obtained for the first time in April 2015 (A–F) indicates the left basal ganglia, thalamus and cerebellum have multiple small circular abnormal signals, the T1WI, T2WI, and FLAIR exhibited low signals in the bilateral basal ganglia and thalamus, and an enhanced scan indicated lesion visible edge enhancements. Semioval center bilateral basal ganglia and other T1WIs indicate multiple punctate or low signals, T2WI high signals, and a FLAIR sequence with a clear display. On the FLAIR sequence, next to the bilateral lateral symmetry, a large sheet of white matter high signal was identified. Next brain MRI obtained in September 2015 (G–K) indicates which compared with April 2015, the right thalamus T2 high signal disappeared. The third MRI obtained in April 2016 (L–Q) indicates multiple punctate susceptibility effects on the SWI sequence in the basal ganglia, which is similar findings with 2015s. FLAIR = fluid-attenuated inversion recovery, MRI = magnetic resonance imaging, SWI = susceptibility-weighted imaging, T2WI = T2-weighted image.

trophic therapy. Her cognitive and movement impairments continuously improved after hormone maintenance therapy. Unfortunately, because of severe osteoporosis, fractures and other adverse reactions, the patient had to terminate prednisone treatment on October 19, 2015. In April 2016, her family members complained that the patient's symptoms seemed to be aggravated, including the unsteady gait and poor memory and comprehension. A neurological examination indicated relatively slow reaction time. Time and spatial disorientation and other cortical dysfunctions were present. The limb muscle tension was increased. Stage 4 myodynamia was observed in the lower limbs, and stage 5 myodynamia was observed in the upper limbs. The patient's gait was unsteady, and her composite feeling was blurred. All four limbs showed a hyperactive tendon reflex; in particular, the ankle jerk reflex on both sides and the deep abdominal reflex on the right side were hyperactive with clonus. The Babinski sign was positive on the right side, and the pathological reflex was negative on the left side. The MMSE score was 21. EEG findings were moderately abnormal (Table 1 and Fig. 3). Antineutrophil cytoplasmic antibodies (ANCA), ESR, and CRP were all normal. The antithyroid antibody levels were as follows: TgAb: 11.69 IU/mL and TpoAb: 532.4 IU/mL (Table 2). The segments from the bilateral auditory nerve to the brain stem were abnormal, as shown by the BAEP. Brain MRI (Fig. 2L–Q) indicated multiple lacunar infarctions, cerebral white matter demyelination, brain atrophy, and multiple punctate susceptibility effects on the SWI sequence in the subcortex and basal ganglia. The patient and her family refused a repeat lumbar puncture once again. The subsequent treatment included improvements in brain metabolism, nutritional support for nerve tissue and relieving excessive muscle tone. On May 2016, the TgAb level was 10.91 IU/mL and the TpoAb level was 562.2 IU/mL (Table 2). We continue to follow the patient regularly, and she continues to undergo symptomatic treatments, such as oral traditional Chinese medicines and cerebral circulation improvement treatments. Currently, the patient can essentially care for herself.

## 3. Discussion

Peschen-Rosin et al[2] described HE diagnostic criteria, including unexplained recurrent myoclonic seizures, comprehensiveness, mental disorder, and focal neurologic deficits, and determined that an HE diagnosis should include at least three of the following five items: abnormal EEG; increased antithyroid antibodies; increased CSF protein; beneficial response to glucocorticoids good; and unexplained head MRI abnormalities. This patient had focal neurologic deficits and cognitive dysfunction. She exhibited significant criteria, such as abnormal EEG, increased antithyroid antibodies, response to glucocorticoids and MRI abnormalities. Thus, based on the above evidence, we consider that this patient definitely suffered from HE.

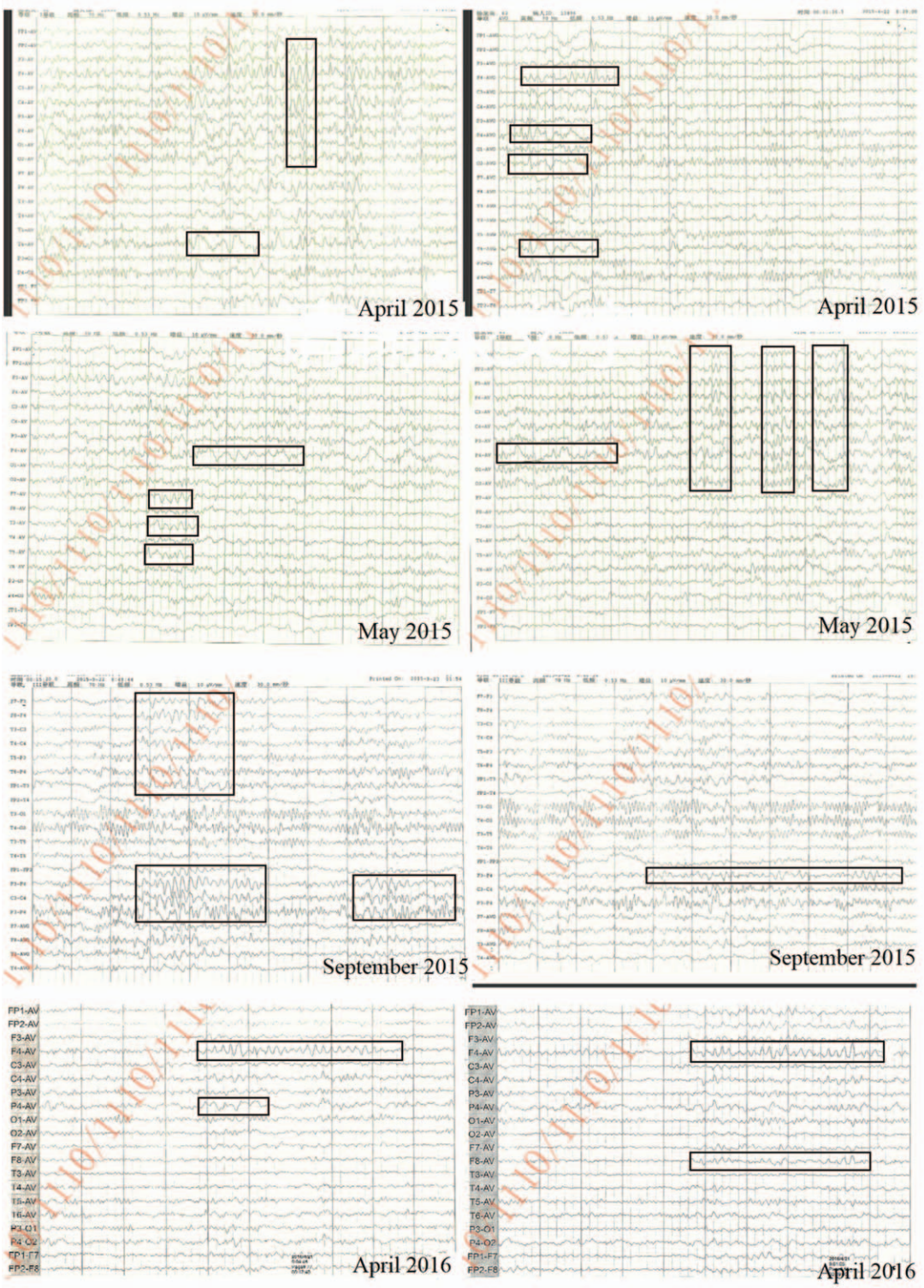


**Figure 3.** Electroencephalogram evolution of the case.

HE was first described in 1966 by Brain et al.[3] An epidemiological analysis determined that the incidence of the disease was 2.1/100,000, and that it primarily affected middle-aged women.[4] The exact pathogenesis of HE remains unclear. HE is associated with a specific autoimmune mechanism[5] that may involve immune complex deposition on the vessel wall, which leads to vasculitis and cerebral hypoperfusion. Another theory implicates hyperthyroid dysfunction combined with intracranial artery stenosis.[6] Thyroid function in patients with this disease may be normal or may manifest as high levels of antithyroid antibodies in the blood, particularly with increased levels of TpoAb and TgAb. The CSF may be normal or exhibit slightly elevated protein. Cell counts may be slightly increased. EEG may indicate an overall slow wave, which is more associated

with clinical symptoms. EEG may also show a three-phase wave, spike wave, spike burst slow wave and slow wave. The patient presented in this report is an elderly woman with hidden onset and gradual progression, who exhibited cognitive decline and walking instability as prominent symptoms. Her cognitive deficits included slight unresponsiveness, memory loss, poor computing power, and declines in understanding and judgment. Her motor symptoms included gait instability, stride length decreases, leg movement difficulty, and decreased ability to walk forward on a flat road. The CSF exhibited moderately elevated immunoglobulins, the EEG examination was abnormal, and the head MRI indicated parenchymal enhancement of multiple abnormal signal shadows. The best characteristic was substantial increases in TgAb and TpoAb titers.

Glucocorticoids remain the first-choice drug for HE treatment. Typically, treatment is initiated with 500 to 1000 mg/d prednisolone shock therapy; after 5 days, oral prednisone 60–80 mg/d is administered for 1 to 6 weeks and is gradually reduced according to the patient's condition. In general, the treatment is maintained for at least 6 months. Some patients with HE develops glucocorticoid resistance; thus, intravenous immunoglobulin or plasma exchange may be effective for these patients. In addition, there are also other immunosuppressants, such as azathioprine, methotrexate, and cyclophosphamide, that have been used to successfully treat HE.[7] After the accepted substantial dose of hormone shock followed by a low-dose hormone dose treatment, the patient's symptoms gradually improved and did not continue to progress; her antithyroid antibodies also gradually declined. A summary of the patient's clinical manifestations and increased antithyroid antibodies indicated that hormone therapy had effectively managed the symptoms and further supported the HE diagnosis. However, in October 2015, the patient's symptoms reappeared following the termination of prednisone. In April 2016, her TpoAb titer was increased again. The patient and her family members refused further immunosuppressive therapy when the potential side effects were fully explained.

CT and MRI imaging of most HE patients indicates no specificity, or MRI may indicate nonspecific T2-weighted imaging (T2WI) and high fluid-attenuated inversion recovery (FLAIR) high signals in brain subcortical white matter areas. If a high signal is restored to normal white matter, this may indicate an improvement.[1] To date, there have not been no magnetic resonance susceptibility-weighted imaging (SWI) sequence reports about HE. In addition to the published reports of cerebral white matter changes, our case report shows that multiple nodal abnormalities in the brain can be detected by the SWI sequence, particularly in the basal ganglia. This interesting MRI finding led us to consider that the patient probably suffered from cerebral small vessel disease (CSVD), such as cerebral amyloid angiopathy (CAA), and related inflammation that is particularly sensitive in SWI sequences of MR.

CSVD refers to clinical, cognitive, imaging and pathological syndromes caused by pathological changes in various types of small blood vessels.[8] The pathology of CSVD, including fibrinoid degeneration, amyloidosis, microhemorrhage, block and other changes, is evidently different from atherosclerosis.[9] Cerebral amyloid vascular lesions (CAA) represent a common form of CSVD with vascular pathological changes; in elderly Chinese individuals, the main pathological characteristics include amyloid beta (Aβ) protein deposition in the cerebral cortex, subcortical regions, pia mater and small blood vessels as well as foreign body deposition.[10] Intracranial vascular Aβdeposition exists in patients with vascular inflammation, which is referred to as CAA-I. CAA-I, a subset of CAA, is an acute or subacute, reversible encephalopathy.[11] In other literature, CAA-I is also referred to as cerebral amyloidosis associated with primary central nervous system vasculitis, amyloid angiopathy of the central nervous system and granulomatous inflammation, cerebral amyloid inflammatory vascular disease, cerebral amyloid vasculitis, and amyloid beta correlation vasculitis.[12] These names indicate the relationship between cerebral amyloidosis and vascular inflammation.

In 1974, Reid and Maloney[13] described cases of Alzheimer's disease (AD) patients and the first discovered cases of CAA with vascular inflammation. Recent studies have indicated that cognitive dysfunctions are the most common clinical manifestations of CAA -I and include memory loss and cognitive dysfunction disuse, executive dysfunctions, and impaired judgment, which ultimately lead to severe dementia and behavioral problems. The second most common manifestations include headache and seizures. Moreover, focal neurologic deficits have been reported.[14] The etiology and pathogenesis of CAA-I are unclear; however, the following 3 features are present: the co-occurrence of blood vessel Aβ protein deposition and vascular inflammation; inflammation-induced vascular Aβ protein deposition; and Aβ protein-triggered vascular inflammation.[15] The pathological features of CAA-I predominantly occur in the cerebral cortex and other regions, such as pia mater cell infiltration, and exhibit granulomatous changes, often accompanied by microscopic bleeding, which may indicate the presence of multiple infarctions.[16] There are no unified and effective treatments for CAA-I; however, in published cases, approximately 80% of patients responded to high-dose hormone therapy or other immunosuppressive therapies with a specific curative effect, which improved the symptoms and imaging lesions.[17] Glucocorticoid treatment improved the symptoms and reduced the elevated ESR, CRP, and IgG titer of CSF, suggesting that this disease is closely associated with inflammation. Thus, the other main diagnostic consideration is CAA-I.

MRI of CAA-I indicates symmetrical or asymmetrical, patchy or confluent high T2 or T2-FLAIR signals with or without edema, and some patients may have meningeal or parenchymal reinforcement. SWI indicates multiple cortical or subcortical microbleeds. These areas are also indicated by the high T2-FLAIR signal associated with microhemorrhage.[14,18] To our knowledge, there has been no systematic study of head CT scans for CAA-I. According to the clinical and SWI sequences features, we consider that the finding of multiple lesions in the basal ganglia region on CT reveals a manifestation of CAA-I associated with microhemorrhage or inflammation.

We boldly propose the following 3 hypotheses:

1. In addition to the MRI manifestations of HE that have been described in the literature, which include nonspecific high T2WI and FLAIR signals in the subcortical white matter areas of the brain, HE may exhibit multiple cortical or subcortical hemorrhages on the SWI sequence. HE is an important risk factor for CSVD, which may include a risk of brain microbleeds. Magnetic resonance SWI sequences help improve the HE microbleed identification rate.
2. HE may occur as a result of the cerebral venous system may occur because of amyloid inflammatory immune complexes; however, this factor must be further investigated via brain biopsies to confirm this hypothesis.

3. In CAA-I cases, amyloid may coexist in the cortex and in the basal ganglia region of the deep brain.

## 4. Conclusion

The diagnosis and treatment of an HE patient with multiple intracranial lesions were described in this case report. Specifically, according to the patient's clinical performance and interesting CT and MRI findings, we simultaneously evaluated her for HE and CAA-I. Three hypotheses were proposed based on the combined presentation of HE and CAA-I. We will continue to follow this patient, review the relevant indicators, and recommend the patient for biopsy for further confirmation at the appropriate time.

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**Resources:** Fan-Xin Kong.
**Supervision:** Fan-Xin Kong.
**Validation:** Zhou-Ke Guo.
**Visualization:** Fan-Xin Kong.
**Writing – original draft:** Fan-Xin Kong, Qing-Hong Lu.
**Writing – review & editing:** Fan-Xin Kong, Zhou-Ke Guo.

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