Pearls & Oysters: Limbic encephalitis associated with positive anti-LGI1 and antithyroid antibodies

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PEARLS Limbic encephalitis is an inflammatory condition of the brain, often characterized by the subacute onset of short-term memory loss, disorientation, seizures, behavioral disturbance, and psychiatric symptoms.

Besides paraneoplastic syndromes with onconeural antibodies targeted against intracellular neuronal antigens, limbic encephalitis may also arise from nonparaneoplastic mechanisms with antibodies targeting neuronal cell surface antigens.

Antithyroid antibodies can be in coexistence with antibodies to neuronal surface antigens such as leucine-rich glioma inactivated protein 1 (LGI1).

IV immunoglobulin (IVIg), plasma exchange, and corticosteroids are all recommended as potential treatment for patients with autoimmune limbic encephalitis with positive anti-LGI1 and antithyroid antibodies.

OY-STERS The differential diagnosis of limbic encephalitis includes glioma, infections, Creutzfeldt-Jakob disease, metabolic disorders, intoxication, and systemic autoimmune disorders.

When limbic encephalitis presents in setting of no fever, meningeal signs, and normal CSF cytology, an autoimmune etiology should be considered.

Antithyroid antibodies, especially antithyroid peroxidase antibody, are common in the general population and often associated with other autoimmune diseases. It is unlikely that antithyroid antibodies themselves are the mediators of limbic encephalitis.

Clinicians should search for the occult tumor and other related autoimmune antibodies before making the diagnosis of Hashimoto encephalopathy.

CASE REPORT A 30-year-old woman with an unremarkable personal and familial medical history was admitted for subacute memory dysfunction of 1 month's duration. She had no recent infection or vaccination. She was not able to remember what had happened on the day she presented or the day before and repeatedly asked the same questions. In addition, she also now enjoyed performing tasks that she previously did not, such as homework. There were

no fevers, seizures, hallucinations, tremor, jerk, or writhing movements during the last month.

On admission, neurologic examination results were normal except for cognitive impairment. The patient's Mini-Mental State Examination (MMSE) score was 20 out of 30. The patient's scores were as follows: orientation to time and place score 4 out of 10, retention score 2 out of 3, calculation and attention score 4 out of 5, recall score 1 out of 3. In addition, her Montreal Cognitive Assessment score was 20 out of 30. The scores were as follows: short-term memory recall task score 0 out of 5, serial subtraction task 2 out of 3, 2-item verbal abstraction task 1 out of 2, orientation to time and place score 3 out of 6. Blood testing, including a complete blood count, coagulation studies, and serum electrolytes, was unremarkable. CSF analysis revealed normal cytology and chemistry. Brain MRI showed hyperintense signal in the bilateral medial temporal lobes and hippocampi on fluid-attenuated inversion recovery imaging (figure). The EEG demonstrated abnormal focal slow wave activity in the temporal region without epileptiform discharges. A diagnosis of limbic encephalitis was established and the empirical treatment with acyclovir was started, considering the presumptive viral infection.

Additional testing was ordered, including CSF microbiological testing (PCR of herpes simplex virus type 1, cytomegalovirus, and measles; Gram stain and acid-fast stain), microbiological serologic testing (herpes simplex virus type 1 and type 2, cytomegalovirus, *Toxoplasma gondii*, measles, HIV, and *Treponema pallidum*), and systemic autoimmune antibodies (anti-dsDNA, anti-SSA, anti-SSB, anti-Sm, anti-RNP, anti-Scl70, anti-Jo-1, p-ANCA, c-ANCA). No positive result was found. Screening for an occult malignant tumor including CT scan (thorax, abdomen, and pelvis), serum tumor markers testing (carcinoembryonic antigen, α -fetoprotein, CA125, CA199, CA724, CYFRA 21-1, neuron-specific enolase, β -subunit of hCG gonadotropin, fetoprotein), and antineuronal antibodies testing (anti-Hu, anti-Ri, anti-Yo, anti-amphiphysin, anti-MA2, anti-CRMP5,

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(A) Fluid-attenuated inversion recovery (FLAIR)-weighted image shows increased signal intensity in the bilateral medial temporal lobes and hippocampi. (B) Gadolinium-enhanced T1-weighted image indicates no pathologic enhancement in temporal lobes and hippocampi. (C) After therapy, FLAIR-weighted MRI shows that the increased signal intensity disappeared.

anti-SOX-1) was also negative. The thyroid serologic testing (free thyroxine 3, free thyroxine 4, and thyroid-stimulating hormone) was also normal, but the antithyroid antibodies levels were elevated. The antithyroid globulin serum level was 61.25 IU/mL (normal 0–4.11 IU/mL) and antithyroid peroxidase was 629.31 IU/mL (normal 0–5.61 IU/mL). In addition, autoimmune encephalitis antibody screening was also requested, including antibodies against NMDA receptor (NMDAR), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), γ -aminobutyric acid receptor B (GABA_BR), and components of voltage-gated potassium channel complex (VGKC) such as LGI1 and contactin-associated protein 2 (Caspr2). Antibodies to LGI1 were positive in both the patient's serum and CSF.

Considering the nonparaneoplastic autoimmune etiology of the limbic encephalitis associated with anti-LGI1 and antithyroid antibodies, the patient underwent further treatment with high-dose IVIg (25 g/d for 5 days). One week after the therapy, she achieved rapid progressive clinical improvement. Her MMSE score was 26 out of 30 with an orientation score of 7 out of 10 and recall score 2 out of 3. Moreover, her Montreal Cognitive Assessment score was 25 out of 30 with short-term memory recall task score 2 out of 5 and orientation to time and place score 4 out of 6. The abnormal signals disappeared on her 3-week follow-up brain MRI (figure).

DISCUSSION Our patient presented with subacute short-term memory loss and behavior changes along with abnormal signals in bilateral medial temporal lobes on MRI, all in accordance with a probable diagnosis of limbic encephalitis. Limbic encephalitis is characterized by the subacute onset of memory loss, disorientation, seizures, behavioral disturbance, psychiatric symptoms, and altered consciousness.¹ It is generally caused by an infectious or autoimmune

etiology. Infectious limbic encephalitis is caused by direct infectious agent invasion, such as herpes simplex virus, rabies, and syphilis. Our patient was initially misdiagnosed with limbic encephalitis caused by herpes simplex virus. Due to the patient's atypical manifestation of viral infection and negative microbiological testing, autoimmune antibodies associated with limbic encephalitis were requested. When a patient presents with limbic encephalitis without fever and meningismus shows normal CSF cytology, an autoimmune etiology should be considered rather than infections. Autoimmune limbic encephalitis caused by the individual's autoimmune reaction against itself was classically described as being paraneoplastic.¹ The onconeural antibodies directed against intracellular neuronal antigens such as Hu, Yo, Ri, MA2, and amphiphysin are usually associated with malignant tumor, including small cell lung cancer, lymphoma, and gynecologic tumor.¹ Recently, reports indicated that autoimmune limbic encephalitis was associated with nonparaneoplastic mechanisms with antibodies targeting neuronal cell surface antigens including VGKC, NMDAR, AMPAR, GABA_BR, mGluR5, and glycine receptors.^{2,3} LGI1 is a secreted synaptic neuronal protein that interacts with presynaptic disintegrin and metalloproteinase domain-containing protein 23 (ADAM23) and postsynaptic ADAM22.⁴ The clinical manifestations of the patient with LGI1 antibody include limbic encephalitis, faciobrachial dystonic seizures, classic tonic seizures, hyponatremia, and sleep behavioral disorders.^{2,5,6} It is unclear whether the association between LGI1 and limbic encephalitis is driven by serum or intrathecal antibodies.

In addition to the evidence of positive LGI1 antibody, our patient also had positive antithyroid antibodies. Antithyroid antibodies are frequently detected in various autoimmune disorders including autoimmune

limbic encephalitis. In association with neurological and psychiatric symptoms, they are often taken as evidence of Hashimoto encephalopathy, also called steroid-responsive encephalopathy associated with antithyroid antibodies.^{7,8} In fact, this entity is a clinically heterogeneous disease that has no definite diagnostic criteria and its etiology is unclear. Recently, several published case reports showed that antithyroid antibodies could be in coexistence with antibodies to neuronal surface antigens such as NMDAR, Caspr2, and LGI1.^{7,9} Our case also supports the previously proposed notion that neuronal and thyroid autoimmunities might represent a pathogenic spectrum.⁸ However, there are no distinguishing clinical features between antithyroid antibody-positive patients with and without antineuronal antibodies.⁷

The course of nonparaneoplastic autoimmune limbic encephalitis tends to be less severe and it is often possible to achieve complete recovery with prompt immunotherapy.^{2,5,10} IVIg, plasma exchange, and corticosteroids are the first-line treatments recommended for limbic encephalitis associated with antibodies targeting neuronal cell surface antigens, whereas Hashimoto encephalopathy is typically steroid-responsive.^{3,6} Since our patient achieved rapid clinical improvement after IVIg and corticosteroid therapy, plasma exchange therapy was not used. As most limbic encephalitis cases associated with LGI1 respond well to immunotherapy, as mentioned above, IVIg, plasma exchange, or corticosteroids should be chosen promptly for the treatment.^{5,6}

Overall, the spectrum of limbic encephalitis is broad. Misdiagnosis inevitably has a negative effect on limbic encephalitis management. The differential diagnoses of autoimmune limbic encephalitis should exclude glioma, infections, Creutzfeldt-Jakob disease, metabolic disorders (uremic, hepatic syndrome), intoxication (alcohol, carbon monoxide), and systemic autoimmune disorders (Sjögren syndrome, systemic lupus erythematosus). Patients who present with limbic encephalitis and have antithyroid antibodies should be screened for other autoimmune processes, rather than label them Hashimoto encephalopathy, as treatment may differ between the 2 groups.

AUTHOR CONTRIBUTIONS

Dr. Sheng-jun Wang was responsible for the analysis of data and drafting of the manuscript. Dr. Yu-ying Zhao was responsible for the interpretation of data and drafting of the manuscript. Dr. Qin-zhou Wang was responsible for analysis of the radiologic data and revision of the manuscript. Dr. Bin Guo was responsible for interpretation of clinical data and revision of manuscript. Dr. Yi-ming Liu was responsible for revision and final approval of the manuscript. Dr. Chuan-zhu Yan was responsible for critical revision and final approval of the manuscript.

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