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Non-tumor-Associated Anti-*N*-Methyl-D-Aspartate (NMDA) Receptor Encephalitis in Chinese Girls With Positive Anti-thyroid Antibodies

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Abstract

Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a new category of autoimmune encephalitis associated with anti-NMDA receptor antibodies. The disease was first described in 2007, and it predominantly affects young women with or without ovarian teratomas. Most patients typically present with seizures, a decreased consciousness level, dyskinesia, autonomic dysfunction, and psychiatric symptoms. The presence of anti-thyroid antibodies in non-tumor-associated anti-NMDA receptor encephalitis was first described in 2010. Additionally, anti-thyroid antibodies were found in teratoma-associated anti-NMDA receptor encephalitis. We report the cases of 3 Chinese girls with non-tumor-associated anti-NMDA receptor encephalitis with positive anti-thyroid antibodies. We followed up the details of their titers and suggest that anti-thyroid antibodies were an indicator of autoimmune predisposition in the development of non-tumor-associated anti-NMDA receptor encephalitis.

Keywords

anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis, anti-thyroid antibodies, chinese adolescents

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Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a recently recognized autoimmune neurologic disorder characterized by severe cognitive impairment, psychiatric symptoms, abnormal movements, seizures, autonomic dysfunction, and coma.[1,2] Recently, several cases have shown that anti-thyroid antibodies coexist with anti-NMDA receptor antibodies in anti-NMDA receptor encephalitis.[3,4] The aim of this study was to assess the role of serum anti-thyroid antibodies in anti-NMDA receptor encephalitis and to provide insight into whether they participate in the pathogenesis of anti-NMDA receptor encephalitis. We report 3 Chinese girls with non-tumor-associated anti-NMDA receptor encephalitis with positive anti-thyroid antibodies, following up the details of these titers. Our clinical profiles suggest that anti-thyroid antibodies should be screened in any unexplained encephalopathy and in anti-NMDA receptor encephalitis.

Case Presentations

Case 1

A 12-year-old girl was admitted to the emergency room complaining of headache, emotional lability, and insomnia for 10 days. One day before admission, the patient had a mild fever. The brain computed tomographic (CT) imaging was normal. At the physical exam, her axillary temperature was 38.7°C, and her pulse rate was 130 counts per minute. She presented with involuntary chewing movements and dystonia. Routine hematologic and biochemical tests showed normal results. The blood cultures, serum tumor markers, serum viral studies, toxicology, and metabolic evaluation did not reveal an abnormality. The contrast-enhanced brain magnetic resonance imaging (MRI), magnetic resonance angiography, and routine ultrasound imaging results were negative. An abdominal CT was unremarkable. An electroencephalogram (EEG) revealed a diffusely slow background, and an

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electrocardiogram (ECG) showed tachycardia. The patient had 3 lumbar punctures, and the cerebrospinal fluid results indicated a mild lymphocytic pleocytosis and a normal protein level. The patient was initially diagnosed with viral encephalitis. An antiviral agent, antiepileptic medication, and antipsychotic drugs were administered. Seven days later, the dysautonomy and fever were improved; however, catatonia, with rigidity, mutism, and waxy flexibility remained. Further evaluation of possible immune-mediated encephalitis, including antinuclear antibodies and antiendomysial antibodies as well as anti-Hu, anti-Yo, and anti-Ri antibodies, produced negative results. The serum anti-thyroglobulin antibody (806.6 IU/mL, normal range 0-115 IU/mL) and anti-thyroid peroxidase antibody (133.1 IU/mL, normal range 0-34 IU/mL) were markedly elevated, and the serum T3, FT3, T4, FT4, and thyroid-stimulating hormone levels and thyroid ultrasonography were normal. On day 15 of the hospitalization, an examination of the serum and cerebrospinal fluid revealed the presence of anti-NMDA receptor antibodies. Intravenous immunoglobulin (0.4 g/kg body weight) was administered for 5 days; intravenous methylprednisolone at a dose of 500 mg was started, followed by 1 month of 1 mg/kg/d oral prednisolone, tapered gradually. Approximately 1 month after admission, the patient became oriented; however, she continued to have slight weakness and slow speech velocity. The serum anti-thyroglobulin antibodies (179.5 IU/mL) and anti-thyroid peroxidase antibodies (87.17 IU/mL) had slightly declined compared with the previous results. The patient was discharged and continued on gradually reduced doses of prednisolone, which was administered for a total of 6 months. Over the following 2 months, the patient improved clinically, and her expression, comprehension, and muscle strength recovered completely. A repeat EEG was normal. The serum anti-thyroglobulin antibodies (91.97 IU/mL) were normal; however, the anti-thyroid peroxidase antibodies (66.99 IU/mL) remained slightly elevated.

Case 2

The patient was a 14-year-old girl, who presented with fever and headache that had lasted over 4 weeks. She developed nausea, vomiting, and fatigue, and 3 weeks later, she became unresponsive and presented with anorexia, irritability, delirium, and psychotic symptoms. Routine blood tests and tumor screening revealed no specific abnormality, and no autoantibodies associated with connective tissue diseases were found. The serum thyroid T3, FT3, T4, FT4, and thyroid-stimulating hormone levels and thyroid ultrasonography were normal. The serum anti-thyroglobulin antibody (423.5 U/mL) and anti-thyroid peroxidase antibody (156.7 IU/mL) levels were markedly elevated. Cerebrospinal fluid examination revealed mild pleocytosis, normal protein, and no oligoclonal band. The ECG showed tachycardia. The MRI and EEG results were negative, and ultrasound imaging showed no evidence of a neoplasm. Initially, intravenous ganciclovir was administered for 3 days as therapy for viral encephalitis. However, her consciousness remained mildly disturbed with concomitant paroxysmal stiff neck, facial twitching, and chewing movement. An additional cerebrospinal fluid and serum test revealed the presence of anti-NMDA receptor antibodies. The patient was treated with intravenous high-dose steroids followed by 1 mg/kg/d of oral prednisolone for 1 month, which was progressively decreased. One month after the steroid therapy, the patient recovered quickly with nearly complete resolution, and the anti-thyroglobulin antibody and anti-thyroid peroxidase antibody levels decreased to the normal range.

Case 3

A 15-year-old girl with no history of systemic disease was hospitalized because of a generalized tonic-clonic seizure following a flulike episode 2 weeks earlier. After initial treatment with antiepileptics and antiviral therapy, her condition deteriorated, and she developed diffuse choreoathetosis and marked agitation as well as severe violent and bizarre behavioral outbursts. Routine blood tests revealed an elevated white blood cell count of 11.9×10^9/L (normal range $3.5\text{-}9.5\times10^9$/L). The serum thyroid T3, FT3, T4, FT4, and thyroid-stimulating hormone levels and thyroid ultrasonography were normal. The test results from tumor and virus screening revealed no specific abnormality, and no autoantibodies associated with connective tissue diseases were found. The serum anti-thyroglobulin antibody (398.3 IU/mL) and anti-thyroid peroxidase antibody (166.2 IU/mL) were remarkably elevated. The cerebrospinal fluid examination only revealed mild pleocytosis. The ECG showed tachycardia. In spite of her history of seizures, repeat EEG testing indicated no seizures. The results of a brain MRI, ultrasound, and abdominal CT were negative. Anti-NMDA receptor antibodies were present in her cerebrospinal fluid and serum, and she was started empirically on intravenous immunoglobulin for 5 days followed by high-dose steroids. Two weeks later, the patient showed significant improvement in her seizure and movement disorders, although she continued to have persistent behavioral problems. The levels of anti-thyroglobulin antibody and anti-thyroid peroxidase antibody decreased to normal range. Two months later, the patient continued to have residual speech problems, although her seizure and movement disorders as well as her psychotic symptoms were greatly improved.

Discussion

In these clinical cases, the patients were girls and presented with prodromal flulike symptoms such as fever and headache, followed by severe psychiatric or behavioral symptoms during all of the disease stages. Psychiatric symptoms typically present within 1 month following prodromal symptoms. All 3 patients had autonomic instability (tachycardia), and 1 of the patients initially presented with frequent seizures. The MRI, magnetic resonance angiography, and routine ultrasound imaging results were

negative. The cerebrospinal fluid results indicated a mild lymphocytic pleocytosis and a normal protein level. Therefore, all of the patients were misdiagnosed with viral encephalitis until anti-NMDA receptor antibodies were demonstrated in the cerebrospinal fluid and serum. During the screening for infectious, autoimmune, and oncogenic factors, we accidently found that serum anti-thyroglobulin antibodies and anti-thyroid peroxidase antibodies were markedly elevated in 3 patients.

The patients did not have a family history of thyroid-associated autoimmune diseases. All of the patients had typical features of anti-NMDA receptor encephalitis and improved after first-line immune therapy,[5,6] The follow-up studies showed that all of the patients fully recovered except the one who had a residual speech problem; none of the patients has had any evidence of neoplasm. Serial dynamic examinations of anti-NMDA receptor antibodies and anti-thyroid antibodies might be useful in clarifying an underlying immune correlation; follow-up anti-thyroglobulin and anti-thyroid peroxidase antibodies in serum was performed 2 months after immunotherapy, and the levels of the 2 antibodies significantly decreased to the normal range. Considering the frequent use of invasive lumbar puncture, we did not follow-up the anti-NMDA receptor antibodies titer.

The presence of anti-thyroid antibodies in non-tumor-associated anti-NMDA receptor encephalitis was first described in 2010.[4] Additionally, the presence of anti-thyroid antibodies were found in teratoma-associated anti-NMDA receptor encephalitis in 2011.[3] Researchers in Turkey found that 33.3% of limbic encephalitis patients had anti-thyroid antibodies, as opposed to 10% to 15% of the general population, and anti-thyroid antibodies are more frequent in patients who have anti-NMDA receptor antibodies.[7,8] The correlation of anti-NMDA receptor antibodies and anti-thyroid antibodies in anti-NMDA receptor encephalitis has yet to be determined. High titers of anti-thyroid antibodies were considered to be the gold standard for the diagnosis of another rare autoimmune disease, Hashimoto encephalitis, which is characterized by neurologic and psychiatric features.[9-11] The most common symptoms of Hashimoto encephalitis include drowsiness, seizures, confusion, dementia, and psychiatric symptoms.[12,13] Anti-NMDA receptor encephalitis and Hashimoto encephalitis share similar clinical features; therefore, the differential diagnosis is difficult if specific antibodies are not screened.[14] Based on our previous clinical experience with Hashimoto encephalitis patients, anti-thyroid antibodies in Hashimoto encephalitis usually increased significantly, and most patients had concomitant diseases of Hashimoto thyroiditis or thyroid dysfunction. In our 3 cases, the patients had no thyroid-associated diseases, and their anti-thyroid antibodies increased mildly or moderately and decreased to normal immediately after immunotherapy. The 3 cases could be diagnosed as anti-NMDA receptor encephalitis complicated with positive anti-thyroid antibodies.

Previous literature based on a large number of patients with anti-NMDA receptor encephalitis indicated that an ovarian tumor could not be found in approximately 40 to 80% of adult patients with the disease.[1,15,16] Nonparaneoplastic presentations are more common in children, adolescents, and male patients.[17,18] Additionally, anti-NMDA receptor antibodies have been detected in patients with herpes simplex viral encephalitis.[19] Herpes simplex viral encephalitis relapse with chorea was associated with autoantibodies to NMDA receptor and the patients showed a clear decline in NMDA receptor antibodies after immune therapy.[20] These evidences suggest that unknown infectious and immunologic triggers might be involved in anti-NMDA receptor encephalitis, separate from the presence of a tumor expressing NMDA receptor, which contributes to the loss of immune tolerance. Our current data demonstrate that patients with positive anti-thyroid antibodies showed trends toward better disease outcomes than patients with negative anti-thyroid antibodies, and these antibodies might suggest a propensity to autoimmunity that may play an important role in non-tumor-associated anti-NMDA receptor encephalitis. It is likely that the abnormal immune reactions activated by the thyroid-associated antibodies secondarily weakened the primary autoimmune state with anti-NMDA receptor encephalitis, which suggested that anti-thyroid antibodies were an indicator of autoimmune predisposition in the development of non-tumor-associated anti-NMDA receptor encephalitis. Our results are consistent with the hypothesis that neuronal and thyroid autoimmunities might represent a pathogenic spectrum.[21] Whether the incidence of anti-thyroid antibodies might cross-react with NMDA receptors, potentially resulting in neuropsychiatric abnormalities, should be assessed in more cases. This study was limited by small numbers and its retrospective nature. Whether these patients develop other autoimmune disorders in the future requires long-term follow-up. The persistence of this finding and the definitive mechanisms behind this observation require further investigation.

Author Contributions

WG and ZF performed the literature search and cowrote the initial draft. HZ, LJ, JL, JZ, HL, JT, and YJ were all part of the clinical team who diagnosed and treated the patient. They all made contributions to the final draft. All authors reviewed and approved the final manuscript. WG and ZF contributed equally to this work.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This study was approved by the Ethics Committee of the First affiliated hospital of Zhengzhou University (2013-50).

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