The Psychiatric Symptoms in Anti-IgLON5 Disease: Case Report and Literature Review

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Key Clinical Message

Immunotherapy may be ineffective in the advanced stages of anti-IgLON5 disease with psychiatric symptoms. The psychiatric symptoms in advanced stages of anti-IgLON5 disease may be associated with neurodegeneration.

Keywords: Anti-IgLON5 disease, Psychiatric symptoms, Neurodegeneration, Immunotherapy, Case report.

Introduction

Recent studies describing patients with autoantibodies against IgLON5, a neuronal cell-adhesion protein, revealed a distinctive sleep disorder, obstructive sleep apnea, gait instability, movement disorders, and brainstem involvement (1, 2). Neuropathological examination demonstrated accumulation of abnormal hyperphosphorylated tau proteins, including 3R and 4R tau isoforms, and neuronal tau deposits in the hypothalamus, the prehypothalamic region, and the tegmentum of the brainstem (1, 3). The HLA-DRB1*10:01 and HLA-DQB1*05:01 alleles have been associated with anti-IgLON5 disease, with this association 36-fold higher than in the general population (4). Moreover, patients with this disease partly responded to immunotherapy (4-6). These findings indicated that anti-IgLON5 disease involves a complex interaction between neurodegenerative and autoimmune mechanisms, with a genetic predisposition (4). It remains uncertain whether anti-IgLON5 disease is an immune disease or a degenerative disease of the nervous system (3, 7-9).

Core symptoms of autoimmune encephalitis include abnormal psychiatric behaviors, cognitive impairment, speech dysfunction, seizures, dyskinesia, autonomic dysfunction, central hypoventilation, and sleep disorders (10-12). Anti-IgLON5 disease differs from autoimmune encephalitis syndromes because of its protracted disease course, deposition of tau, and variable effect of immunotherapy, making it challenging to diagnose and treat (3). A previous study found that IgLON5 antibodies were not common in a population of patients with first-episode psychosis or a clinical high-risk for psychosis (13). However, anti-IgLON5 disease can also have psychiatric symptoms, with these symptoms appearing at onset in some cases, and during the course of disease in others (14). Few previous studies had summarized and analyzed the psychiatric symptoms of anti-IgLON5 disease. Here, we presented a case with psychiatric symptoms in the advanced stage and reviewed relevant literature to explore the clinical manifestations, treatment, and outcomes of anti-IgLON5 disease with psychiatric symptoms.

Case presentation

A 63-year-old man came to our hospital with the first-presenting psychiatric symptoms (confusion, gibberish, grabbing things aimlessly, and relieving himself at will). At 5 years earlier, the initial symptoms were mild
dysphagia, mild dystonia and sleep disturbances (shouting during sleep). Although the patient had visited the hospital, patient’s disease remained undiagnosed. At this time, we found he also had bulbar dysarthria, dysphagia, oculomotor dysfunction (restriction of vertical and horizontal gaze), sleep disturbances (shouting and sleep attacks, which disappeared when waking up), dystonia, restriction of neck rotation. (Fig. 1A).

Neurological examination revealed horizontal and vertical gaze palsy, restricted mouth opening, reduced gag reflex, dysarthria, restriction of neck rotation, mild dystonia of both lower extremities, active tendon reflexes in the extremities, and Babinski’s sign in his lower-right extremity. Blood test results showed that immunity, comprehensive metabolism, endocrine, and infection were normal. Blood gas analysis was normal. Brain and brainstem magnetic resonance imaging (MRI) were normal. Tumors were ruled out using chest and abdomen computed tomography and nasopharyngeal-region MRI. His electroencephalogram study was normal but electromyography revealed extensive neurogenic damage. Cerebrospinal fluid examination was performed because of the psychiatric symptoms. CSF tests revealed normal nucleated cells and protein. Infectious-disease studies showed negative results for virus, cryptococcus, tuberculosis, bacteria, and fungi. Investigations of paraneoplastic and autoimmune antibodies were performed by collecting antibodies from the patient’s serum and CSF, included antibodies to LGI, GABAB receptor, NMDA receptor, Caspr2, AMPA1 receptor, AMPA2 receptor, DPX, IgLON5, GAD65, GlyR1, DR2, mGluR5, Hu, Yo, Ri, CV2, Ma2, amphiphysin, Ma1, SOX1, Tr (DNER), Zic4, GAD65, PKCy, recoverin, and titin. Only the anti-IgLON5 antibody test was positive in both CSF and serum (1:320 and 1:100, respectively; Fig. 1B).

The patient was started on treatment with intravenous immunoglobulin (IVIg) (2 g/kg for 5 days) followed by high-dose steroid therapy (1 g/day for 5 days and gradually reduced). Olanzapine was used temporarily when psychiatric symptoms were severe in the initial stages. One month later, only the abnormal psychiatric behaviors showed any improvement. The patient’s other symptoms became worse during the 34 weeks of follow-up.

Review of previously reported cases of anti-IgLON5 disease with psychiatric symptoms

Including our patient, 18 cases were eligible for our review (Table 1) (Supplementary Method). Of those, eight patients were male and 10 were female, and the age at diagnosis ranged from 45 to 84 years (average 65 years). The average time from symptom onset to diagnosis was 25 months. For CSF testing, 17 patients had anti-IgLON5 antibody, and 13 patients had anti-IgLON5 antibody with their serum tested. Of 11 patients, three displayed abnormal brain MRI. But of the 15 patients, six had abnormal nucleated cells and/or protein. In terms of psychiatric symptoms, eight patients displayed confusion, seven patients displayed depression, six patients had hallucinations, two patients had delirium, two patients displayed abnormal behaviors, and one patient displayed anxiety. The average time of psychiatric symptoms present was 13 months (range 0–60 months). Among the 12 patients who had received immunotherapy (including steroids, IVIg, plasma exchange, or immunity inhibitors), six partially improved, one fully improved, and five had no improvement.

Discussion

Anti-IgLON5 disease is mainly characterized by sleep disorders, bulbar dysfunction, gait instability, obstructive sleep apnea, movement disorders, oculomotor dysfunction, and neuropsychiatric symptoms (3, 14). Our patient also displayed bulbar dysarthria, dysphagia, oculomotor dysfunction, sleep disturbances, movement disorder, and restriction of neck rotation, with definite abnormal physical signs in the nervous system. Antibody testing was performed because of the psychiatric symptoms, and anti-IgLON5 disease was finally diagnosed. Only the abnormal psychiatric behaviors improved after treatment with IVIg, high-dose steroids and olanzapine.

Patients with autoimmune encephalitis often have abnormal psychiatric behaviors, including decreased or altered level of consciousness, lethargy, or personality change (11), and the abnormal psychiatric behaviors often present at an early stage. However, our patient developed psychiatric symptoms after 60 months, and the patient’s symptoms were not diagnosed in the past five years because the neurological symptoms were mild. Our literature review found that the psychiatric symptoms of anti-IgLON5 disease not only present at onset, but during the course of the disease. Therefore, the psychiatric symptoms of anti-IgLON5 disease
are different from autoimmune encephalitis syndromes, patients with neurological symptoms and late onset of psychiatric symptoms need to consider anti-IgLON5 disease.

Research has demonstrated that neuronal 3R- and 4R-tauopathy mainly involves the brainstem and hypothalamus in anti-IgLON5 disease (1, 2, 15). Both Aβ(1-42) and pathogenic P-tau significantly induced learning and memory deficits and enhanced anxiety behavior in adult male rats (16). Tau-P301L transgenic mice showed decreased cognitive flexibility in the morris water maze, decreased exploratory behavior, and increased anxiety-like behavior (17). Participants with elevated tau were twice as likely to be depressed in previous study (18). Moreover, hallucinations are also associated with more severe cognitive impairment in Alzheimer’s disease (19), and can be visual or auditory (20). A previous study revealed that increased baseline hallucinations, apathy, and anxiety were associated with current and future disease progression in Alzheimer’s disease (19). Literature review showed that some patients with psychiatric symptoms had normal nucleated cells and protein in CSF. Our patients also had normal nucleated cells and protein in CSF. Moreover, brain and brainstem magnetic resonance imaging were normal in our study. Our literature review also displayed that the brain MRI of some patients were normal. A previous study found that cultures exposed to anti-IgLON5 antibodies showed reduced neuronal spike rate and synaptic protein content, and a higher proportion of neurons with degeneration, including p-tau positive neurons, indicating that pathological anti-IgLON5 antibodies induced neurodegenerative changes and cell death in human neurons (21). Therefore, we speculated that the normal brain MRI and psychiatric symptoms in our patient might be associated with neurodegeneration of anti-IgLON5 disease.

Although some patients with IgLON5 antibodies were responsive to immunotherapy, consistent with most other forms of neuronal cell-surface autoantibody-mediated diseases (22, 23), patients with improvement in symptoms still require long-term follow-up because symptoms may worsen and patients may die suddenly (1, 14, 24, 25). Gruter et al. found that first-line immunotherapy of relapse-like acute-to-subacute exacerbation episodes resulted in improvement in 41% of patients and early immunotherapy (before advanced neurodegeneration) was associated with a better long-term clinical outcome (26). In cultures of hippocampal neurons, antibodies of patients caused a decrease in cell-surface IgLON5 clusters that was not reversed after IgLON5 antibodies were removed from the media, indicating an irreversible antibody-mediated internalization of surface IgLON5 in hippocampal neurons (27). In our patient, only the abnormal psychiatric behaviors showed improvement with immunotherapy, but the patient’s other symptoms did not improve. These may suggest neurodegeneration of anti-IgLON5 disease respond poorly to immunotherapy, and it is important to diagnose anti-IgLON5 disease early for patients. The improvement of our patient’s psychiatric symptoms may be associated with antipsychotics.

There were several limitations in our study. First, although causes of psychiatric symptoms (e.g., tumor, metabolism, immunity, infection, and endocrine) were excluded in our case, it cannot be fully ruled out that psychiatric symptoms were related to the consequence of other aggravated symptoms. Second, videopolysomnography and detailed neuropsychological assessment were not performed in our study.

In general, the psychiatric symptoms of anti-IgLON5 disease can present not only in the early stages of the disease, but also in the advanced stages. The psychiatric symptoms may be associated with neurodegeneration in our patient. Immunotherapy may be ineffective in the advanced stages of anti-IgLON5 disease. Therefore, it is necessary to consider anti-IgLON5 disease when for patients with psychiatric symptoms and neurological symptoms.

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Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics approval
This report was approved by the Ethics Committee of Sichuan Provincial People’s Hospital.

Consent statement

The participant has consented to the submission of the case report to the journal.

Author Contributions

Yuanyuan Luo had made substantial contributions to drafting/revision of the manuscript for content, acquisition of data, analysis or interpretation of data and study design. Jun Xiao and Jieying Li had made contributions to study design.

References


**Figure legends**

**Fig. 1.** Clinical characteristics of our patient with anti-IgLON5 disease. Upper part of Figure 1A shows the symptoms; middle shows the time and the treatment, and lower part shows the examination. Only the abnormal psychiatric behaviors were improved with steroid, IVIg and olanzapine treatment. The left part of Figure 1B shows the immunoactivity of the anti-IgLON5 antibodies in CSF (1:320), and the right part shows anti-IgLON5 antibodies in serum (1:100) (original magnification × 200).

**Table legends**

**Table 1.** Clinical features of anti-IgLON5 disease with neuropsychiatric symptoms.
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Table 1.DOCX available at https://authorea.com/users/645644/articles/657964-the-psychiatric-symptoms-in-anti-iglon5-disease-case-report-and-literature-review