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Acute onset of anti-IgLON5 disease with meningeal enhancement: a case report

Huasheng Huang[1], Yizhi Wei[1] and Jie Li[1,2*]

Abstract

Background Anti-IgLON5 disease is a relatively rare autoimmune disease of the nervous system. The clinical course of this disease is generally chronic and progressive, exhibiting heterogeneity in clinical presentation and the lack of specific imaging features. We now report a case of a Anti-IgLON5 antibody-positive patient demonstrated two distinctive features. Firstly, the onset was marked by acute encephalopathy symptoms, including fever, with consciousness disturbance as the initial manifestation. Secondly, imaging studies revealed multiple lesions within the meninges and intracranial regions, characterized by extensive thickening and enhancement of the dura mater.

Case presentation A previously healthy 78-year-old male patient presented with impaired consciousness and was admitted to the hospital. Brain MRI demonstrated abnormal signal located in the bilateral basal ganglia, frontal and parietal lobes. Post-contrast enhancement demonstrated thickening and enhancement of the dura mater in the bilateral frontal regions, along with mild enhancementin the cortical areas of the bilateral temporal lobes. Cerebrospinal fluid (CSF) analysis indicated the presence of oligoclonal bands in both serum and CSF, with a higher count in the CSF compared to serum. IgG antibodies against IgLON5 were detected in serum and CSF at a titer of 1:100. CSF concentrations of total Tau protein (t-Tau) and phosphorylated Tau protein (p-Tau) were normal. In conjunction with a positive serum and CSF IgLON5 antibody and exclusion of other diseases, diagnosis of anti-IgLON5 disease was made. Symptoms resolved completely after intravenous methylprednisolone and immunoglobulin therapy were administered. At 3-week follow-up the small patchy abnormal signal in the bilateral basal ganglia, frontal and parietal lobes have resolved. Additionally, post-contrast imaging reveals the absence of the previously noted abnormal dural enhancement. and there was no recurrence 18 months after the onset of the disease.

Conclusions Anti-IgLON5 disease is a heterogeneous disorder characterized by a wide spectrum of clinical manifestations. IgLON5 encephalopathy characterized mainly by symptoms of acute neurological symptoms and MRI evidence of meningeal enhancement has not been reported previously. The appropriate diagnostic strategy should encompass a thorough clinical evaluation, testing for anti-IgLON5 antibodies in both CSF and serum, as well as HLA genotyping. Timely diagnosis and early Intravenous methylprednisolone and/or IVIG therapy are beneficial in improving prognosis and preventing recurrence.

Keywords Anti-IgLON5 antibody, Autoimmune encephalitis, Immunotherapy

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Foreword

Anti-immunoglobulin-like cell adhesion molecule 5 (IgLON5) disease is a relatively rare autoimmune disease of the nervous system. In 2014, Sabater et al. [1] reported 6 patients with presenting with IgLON5 antibodies, sleep disturbances, and tau protein deposition. Since then, an increasing number of cases have been reported, highlighting the heterogeneity of clinical manifestations, including sleep dysfunction, medullary dysfunction, choreiform movements, and cognitive impairments. The clinical course of this encephalopathy is generally chronic and progressive, exhibiting considerable individual variability in clinical presentation. This paper aims to present a rare case of anti-IgLON5 antibody-associated encephalopathy, characterized by acute onset and involving both meningeal and brain parenchymal damage. Clinically, the case is marked by a rapid progressive decline in consciousness and atypical inflammatory lesions observed on brain magnetic resonance imaging (MRI). Notably, the patient exhibited a favorable response to immunotherapy. This case contributes to the expanding understanding of the disease's clinical manifestations and provides valuable insights for both diagnosis and research.

Case report

A 78-year-old male patient was admitted to the hospital on March 28, 2023 for "impaired consciousness for 9 days". Nine days prior to admission, the patient was found in a state of altered consciousness by the roadside after being outdoors at noon. Initial symptoms included confusion, mild delirium, a fever of 40.0 °C, the patient had no vomiting, no limb convulsions, and no urinary or fecal incontinence. Upon evaluation at a local hospital, the physical examination indicated a comatose state with a Glasgow Coma Scale (GCS) score of 7 (E1V1M5), occasional agitation, pupils that were equal and round with a diameter of 2.5 mm, sluggish light reflexes, and neck stiffness. Auxiliary examination results revealed the following: blood routine analysis indicated a white blood cell count of 12.60 × 10^9/L and neutrophils at 85.0%. There were no significant abnormalities detected in glucose levels, cardiac enzymes, blood gas analysis, liver and kidney function, blood sugar, electrolytes, or coagulation function. Tests for syphilis and HIV were negative. CT scan of the head showed bilateral lacunar cerebral infarction in the basal ganglia region, with demyelination of the white matter. A lumbar puncture performed on March 19, 2023, showed the CSF pressure of 180 mmH2O. The CSF was pale yellow and slightly turbid, with a white blood cell count of 755.0 × 10^6/L, comprising 89.90% monocytes and 10.20% polymorphonuclear cells. The glucose level in the CSF was 2.61 mmol/L, and protein was not detected. Considering the possibility of central nervous system infection, the patient received treatment with acyclovir (0.5 g, q8h, IV infusion), ceftriaxone (2 g, q12h, IV infusion), along with symptomatic supportive care. After nine days of treatment, the patient's level of consciousness improved to a drowsy state, the patient was transfer to a tertiary comprehensive hospital for further diagnostic evaluation and management. Upon admission to the new hospital, the physical examination findings included: a drowsy state, poor cooperation with advanced cognitive testing, simple responses, dysarthria, hoarseness, and a diminished pharyngeal reflex. No ocular movement disorders were observed. Pupils were equal and round, 3 mm in diameter, with sensitive light reflexes. Muscle strength evaluation indicated an approximate grade of 4 in both upper limbs, grade 2 in the left lower limb, and grade 3- in the right lower limb. Muscle tone across all limbs was reduced, accompanied by diminished tendon reflexes. The patient exhibited fecal incontinence and a decreased pain sensation in the region extending from the anal area to the sacrum (approximately 10 cm). The anal reflex was absent, Babinski signs were negative bilaterally, and there was resistance in the neck. The patient presents with a 10-year history of hypertension, with a recorded maximum blood pressure of 160 mmHg and inconsistent adherence to prescribed medication. There is no reported history of epidemiological exposure. Over the past year, the patient has experienced sleep disturbances characterized by frequent somniloquy and involuntary movements, including raising hands, grabbing objects, shouting, and singing. Relevant auxiliary examinations revealed the following: Complete blood count showed a white blood cell count of 13.11 × 10^9/L (elevated), a lymphocyte percentage of 7.8% (decreased), and a neutrophil percentage of 86.8% (elevated). Additionally, C-reactive protein was measured at 108.90 mg/L (elevated), and the erythrocyte sedimentation rate was 58 mm/h (elevated). No significant abnormalities were detected in the blood ANCA antibody, antinuclear antibody profile, anti-O, rheumatoid factor, blood glucose, and blood bacterial culture tests. Considering that paraneoplastic syndrome may be a potential cause of autoimmune encephalitis, we routinely screened the patient's chest CT and performed hematological examinations for tumor markers (see supplementary data). No definite evidence of tumors was found. Lumbar puncture performed on March 30, 2023, revealed an intracranial pressure of 60 mmH_2O. The CSF was light red in color and slightly turbid, with a glucose concentration of 2.83 mmol/L, a protein quantification of 1.52 g/L, and a white blood cell count of 220 × 10^6/L, predominantly mononuclear cells (99.5%) with a minor fraction of polynuclear cells (0.5%). Because the patient had fecal incontinence and decreased pain sensation, in order to rule out spinal cord lesions, we also carried out an examination of the spinal MRI. The results indicated degeneration and protrusion of the

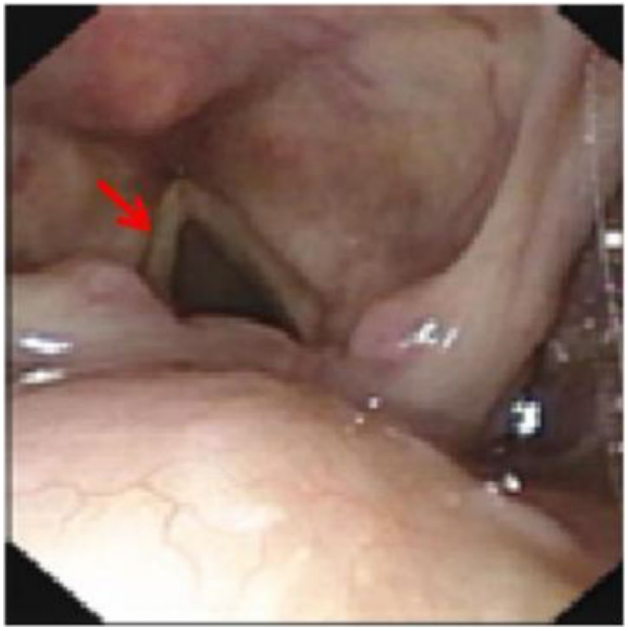

Fig. 1 Laryngoscopy revealed smooth bilateral vocal cords, with fixation of the left vocal cord and satisfactory movement of the right vocal cord

cervical intervertebral discs, and spinal cord degeneration at the C3/4 level. No definite lesions were found in the thoracic and lumbar spinal cord (see supplementary data). Electromyography findings included: (1) damaged of the right superficial peroneal nerve, and (2) decreased motor conduction amplitude in both lower limbs. Laryngoscopy revealed smooth bilateral vocal cords, with fixation of the left vocal cord and satisfactory movement of the right vocal cord (Fig. 1). A brain MRI, including both plain scan and contrast enhancement conducted on March 31, 2023, demonstrated diffuse thickening and enhancement of the dura mater, as well as nodular abnormal signals in the right frontal lobe, bilateral temporal lobes, and left insular lobe (Fig. 2A-D). CSF analysis indicated the presence of oligoclonal bands in both serum and CSF, with a higher count in the CSF compared to serum, suggesting intrathecal synthesis and disruption of the blood-brain barrier. Serum IgG4 levels were negative. Following the transfer to the new hospital, the patient continued to receive antiviral treatment with acyclovir, infection control with ceftriaxone. Despite 6 days of treatment, the patient persisted with intermittent fever and showed no significant improvement in condition. Further analysis of CSF using metagenomic next-generation sequencing (mNGS) revealed 39 reads of Epstein-Barr virus (EBV). Additionally, IgG antibodies against IgLON5 were detected in serum at a titer of 1:100, among the 20 items tested for autoimmune encephalitis(including NMDA, AMPA1, AMPA2, LGI 1, CASPR2, GABAB, DPPX, GlyR1, DRD2, GAD65, mGluR5, IgLON5, mGluR1, Neurexin-3a, GABAA,

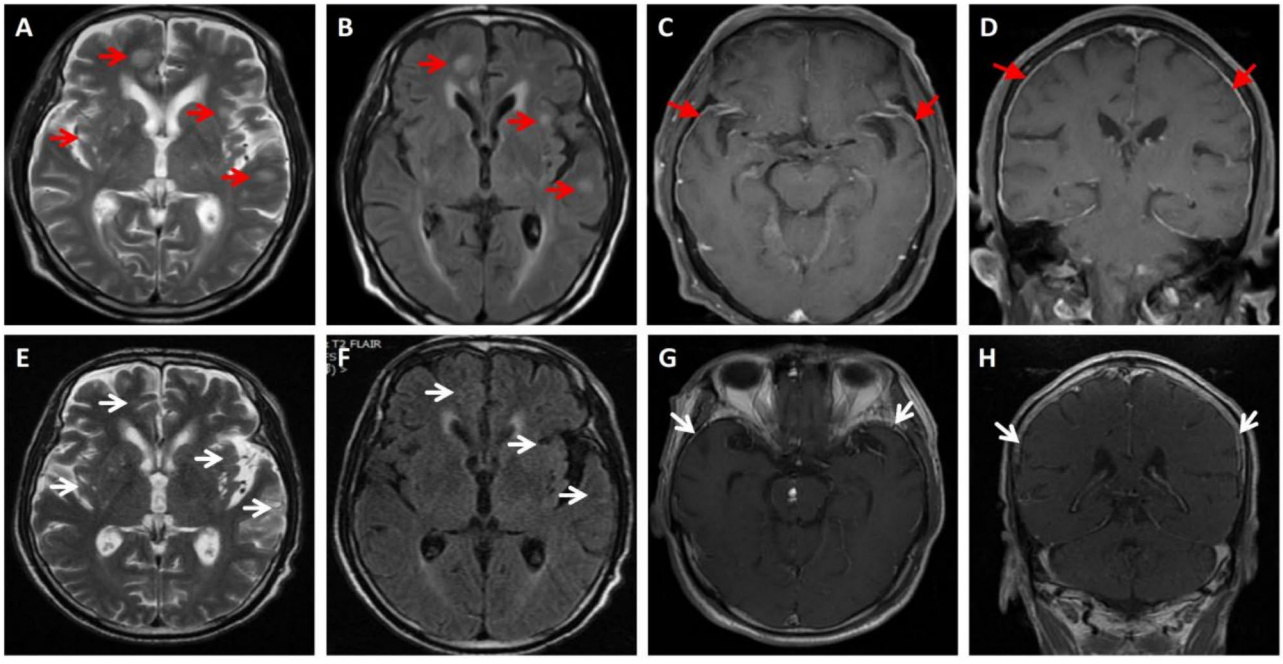

Fig. 2 **A-D**: The brain MRI scan revealed small, patchy abnormal signal foci located in the bilateral basal ganglia, frontal and parietal lobes, and periventricular regions. These foci exhibited high signal intensity on T2-weighted and FLAIR imaging. Post-contrast enhancement demonstrated thickening and enhancement of the dura mater in the bilateral frontal regions. **E-F**: In comparison to the prior scan, the small patchy abnormal signal foci in the bilateral basal ganglia, frontal and parietal lobes, and periventricular regions have resolved. Additionally, post-contrast imaging reveals the absence of abnormal dural enhancement

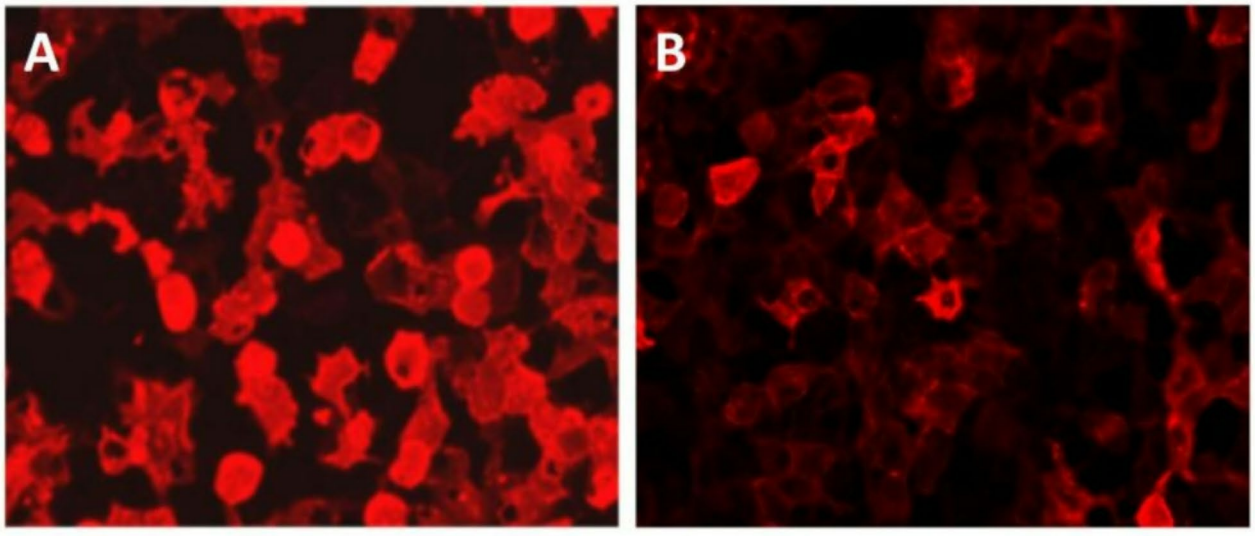

Fig. 3 Detection of anti-IgLON5 Antibody IgG. (**A**) An indirect immunofluorescence assay utilizing cell based assay method demonstrate an immunofluorescent reaction between the patient's CSF and IgLON5-transfected cells at a dilution of 1:100. (**B**) Subsequent re-evaluation of IgLON5 antibody IgG reveals a reduction in titer to 1:10

KLHL11, ganglionic AChR, AQP4, MOG, GFAP antibodies). The CSF also tested positive for anti-IgLON5 antibody IgG at the same titer of 1:100 (cell based assay, Fig. 3A). After the positive identification of IgLON5 antibodies, the treatment regimen was modified. Specifically, antiviral therapy was discontinued, and a course of methylprednisolone (500 mg IV drip for 5 days, followed by a gradual taper) along with intravenous immunoglobulin (IVIG, 0.4 g/kg for 5 days) was initiated. To further clarify the diagnosis of anti-IgLON5 antibody-related encephalitis, additional evaluations were performed. The HLA allele analysis revealed the presence of the following alleles: HLA-DRB1*11:01, HLA-DRB1*15:01, HLA-DQB1*03:01, and HLA-DQB1*06:02. CSF concentrations of total Tau protein (t-Tau) and phosphorylated Tau protein (p-Tau) were quantified at 477.39 pg/ml and 30.60 pg/ml, respectively, utilizing the ELISA method, with no elevations observed. Following three days of treatment with methylprednisolone and IVIG, the patient's body temperature normalized, and clinical condition progressively improved. After twenty days, the patient regained consciousness and was able to stand with assistance. The physical examination indicated impaired memory, normal swallowing function, a mildly hoarse voice, muscle strength graded at level 4 in the right lower limb and level 3 in the left lower limb, and no resistance in the neck. The Mini-Mental State Examination (MMSE) score was 20. Subsequent analysis of CSF revealed a protein concentration of 0.75 g/L and a white blood cell count of $12 \times 10^{\wedge}6$/L. A follow-up CSF test for anti-IgLON5 antibodies IgG (1:10) returned positive on April 17, 2023 (cell based assay, Fig. 3B). A contrast-enhanced brain MRI conducted on April 18, 2023, demonstrated the resolution of previously observed brain parenchymal nodules and no abnormal meningeal enhancement (Fig. 2E-H). After being discharged from the hospital, the patient was additionally treated with tacrolimus. Subsequent follow-up (July 5, 2024) shows that the patient's muscle strength is within normal limits, cognitive function has shown improvement, and MMSE score is 28. Additionally, family members reported an absence of sleep disorders in the patient.

Discussion

Anti-IgLON5 disease is classified within the spectrum of autoimmune diseases associated with neuronal surface proteins and is characterized by highly heterogeneous clinical manifestations. The primary symptoms encompass sleep disorders, medullary symptoms such as abnormal gait, and cognitive impairment. Additionally, common symptoms include ocular nerve abnormalities, such as vertical/horizontal gaze palsy, nystagmus. An increasing number of case reports have shown that there are symptoms of the peripheral nervous system, such as autonomic nervous system dysfunctions, including nocturia, urinary urgency, anhidrosis, or constipation. Other rare ones include hyperhidrosis, orthostatic hypotension, autonomic cardiac dysfunction accompanied by ventricular tachycardia or severe bradycardia [2, 3]. Hyperexcitability of the peripheral nervous system includes excessive startle response, stiffness, spasms or fasciculations and vestibular nerve disorders [3–5]. A minority of cases may present with psychiatric symptoms such as hallucinations or seizures. The disease generally follows

a chronic course with a gradual onset; however, rare instances of subacute or even acute onset (ranging from days to two weeks) have been reported [6]. The symptoms typically persist for several years.

In this case, the patient presented with impaired consciousness, fever, sleep disturbances, and bulbar symptoms. Based on the patient's symptoms, it is considered that REM Sleep Behavior Disorder (RBD) is possible. Auxiliary tests revealed positive serum and CSF anti-IgLON5 antibodies, thereby confirming a diagnosis of anti-IgLON5 disease. Compared to previously documented cases of anti-IgLON5 disease, this patient demonstrated two distinctive features. Firstly, the onset was marked by acute encephalopathy symptoms, including fever, with consciousness disturbance as the initial manifestation. Secondly, imaging studies revealed multiple lesions within the meninges and intracranial regions, characterized by extensive thickening and enhancement of the dura mater. These findings were accompanied by leptomeningitis and abnormal nodular signals in the right frontal lobe, bilateral temporal lobes, and left insula. In this case, 9 days after antiviral treatment, magnetic resonance suggested dural thickening and enhancement of the cerebral cortex meninges and parenchymal lesions. In contrast, after discontinuing antiviral treatment and switching to high-dose methylprednisolone and IVIG, the intracranial lesions completely disappeared. In this case it is highly likely that the patient's febrile symptoms were caused by the acute onset of IgLON5 encephalitis. However, the possibility of its association with Epstein-Barr virus infection cannot be excluded. Antiviral drugs were also used during the treatment process. Wang et al. [7]reported a case of anti-IgLON5 encephalopathy concurrent with herpesviral encephalitis in a 51-year-old male patient. The patient presented with acute encephalitis, mental disorder, and memory impairment, and was found to be positive for HLA-DQB1*05:01 and HLA-DRB1*10:01. Human α herpesvirus type 1, EB virus, and IgLON5-IgG were detected in the CSF, suggesting that the patient had anti-IgLON5 encephalopathy with herpesvirus encephalitis. The patient's condition improved after treatment with antiviral drugs, IVIG, and methylprednisolone. Low copy number EBV detected in CSF, may also come from latently infected lymphocytes, has been reported in some patients with co-infection (such as streptococcus pneumoniae, cryptococcus, mycobacterium tuberculosis, herpes simplex virus type 1, varicella-herpes zoster virus, etc.), its EBV nucleic acid can reach tens of thousands of copy/ml, but it is difficult to determine whether it is involved in pathogenicity. The patient's condition improved after antiviral treatment, and the lesion of MRI brain parenchymal nodules disappeared, and he still had dural thickening and leptomeninges enhancement of the cerebral hemisphere, but failed to fully recover from it. In contrast, the intracranial lesions were completely resolved after withdrawal of antiviral therapy and replaced by methylprednisolone and IVIG therapy. In rare cases, patients have shown improvement without immunotherapy. For example, a report describes a 62-year-old man whose serum analysis confirmed the presence of IgLON5 antibodies, with HLA-DQB 1 * 05:01 and HLA-DRB 1 * 10:01 positive. The patient's symptoms improved and antibody titers decreased after antiviral treatment alone, without the use of immunotherapy. This suggests that viral infection may play a role in the pathogenesis of IgLON5 antibody-related encephalopathy [8]. In this case, CSF mNGS testing indicated 39 reads of Epstein-Barr virus (EBV). EBV infection has been reported in many cases [4], and it is considered a potential triggering factor, although the exact mechanism is not yet determined. After infecting the human body, EBV can integrate its nucleic acid into the chromosomes of B cells, thus persisting within the individual's B cells. The low copy number of EBV detected in the CSF may also originate from latent-infected lymphocytes. Reports indicate that in some co-infected patients (e.g., with Streptococcus pneumoniae, Cryptococcus, Mycobacterium tuberculosis, herpes simplex virus type 1, varicella-zoster virus, etc.), EBV nucleic acid levels can reach tens of thousands of copies/ml, but its role in pathogenesis is still uncertain.

Anti-IgLON5 disease is hypothesized to induce neurodegeneration in distinct regions of the central nervous system, with neuropathological manifestations predominantly involving the brainstem, hypothalamus, and perihippocampal areas, characterized by tau phosphorylation and deposition [9]. Imaging studies indicate that approximately 95% of patients exhibit normal or nonspecific alterations on MRI, including localized lesions in the frontal, parietal, occipital, and temporal lobes, brainstem, hippocampus, amygdala, and hypothalamus. A minority of patients demonstrate specific changes, such as atrophy of the hypothalamus, brainstem, and cerebellum [2, 10, 11].

Notably, most of the changes detected on MRI are localized to regions impacted by tauopathies. Contrarily, our case demonstrated pronounced, diffuse thickening and enhancement of the dura mater, along with leptomeningitis and abnormal nodular signals in the right frontal lobe, bilateral temporal lobes, and left insular lobe. Existing research suggests that the neuropathology of anti-IgLON5 disease is time-dependent, with tau pathology typically occurring in the later stages of the disease, primarily affecting the brainstem and cerebellum [12, 13]. Anti-IgLON5 antibodies may precede tau pathology, and early initiation of immune therapy can prevent irreversible neuronal damage and disease progression [14]. In this case, CSF levels of total tau protein (t-Tau) and

phosphorylated tau protein (p-Tau) were 477.39 pg/ml and 30.60 pg/ml (ELISA), respectively, with no elevation observed. We believe that this patient primarily presents with the immune encephalopathy phase related to anti-IgLON5 antibodies. If the disease is not well controlled, the corresponding imaging manifestations of the brainstem and cerebellum may appear in the later stages of the disease. Following treatment with corticosteroids and immunoglobulins, the patient's symptoms significantly improved, with anti-IgLON5 antibody titers decreasing from 1:100 to 1:10, and MRI showing resolution of abnormal brain signals and meningeal enhancement. All of these findings suggest that the patient's symptoms may be related to the titer of anti-IgLON5 antibodies, which could play a critical role in the pathogenesis. In this context, early diagnosis and treatment are crucial for delaying or even preventing the progression of the presumed pathological mechanisms. Prompt intervention with immunotherapy may alter the outcome of anti-IgLON5 disease.

Research has demonstrated a significant association between the human leukocyte antigen (HLA) alleles HLA-DQB1*05:01 and HLA-DRB1*10:01 and the presence of anti-IgLON5 antibodies, thereby supporting the genetic susceptibility hypothesis in the pathogenesis of autoimmune diseases [4, 15, 16]. In the present case, the patient's HLA genotyping confirmed the presence of HLA-DRB109:01, HLA-DRB115:01, HLA-DQB103:03, and HLA-DQB106:01 alleles, but did not show the same genetic susceptibility alleles (HLA-DQB105:01 and HLA-DRB110:01) reported in previous studies. However, the HLA-DRB1*09:01 [17]and HLA-DRB1*15:01 [18]alleles identified in this patient have also been reported in the literature previously.

Anti-IgLON5 antibody-associated encephalopathy presents with both immune and degenerative pathological changes. Compared to other autoimmune encephalitis-related antibodies, basic research suggests that IgLON5 antibody-induced neuronal damage and degeneration are irreversible, indicating a potential link between autoimmunity and neurodegeneration in anti-IgLON5 disease. Regarding the effectiveness of immunotherapy, there is currently no consensus. Although some reports suggest immunotherapy is ineffective, most believe treatment should be initiated early [19]. The most common treatments for anti-IgLON5 antibody-associated encephalopathy include intravenous corticosteroids, IVIG, therapeutic plasma exchange (TPE), rituximab, cyclophosphamide, azathioprine, and mycophenolate mofetil. Combination therapy and second-line treatments appear to be more effective than monotherapy [20, 21]. In this case, the patient received methylprednisolone and IVIG treatment, and showed significant improvement in consciousness level and a decrease in anti-IgLON5 serum titer from 1:100 to 1:10. Studies suggest that the remission of neurological symptoms may be related to the reduction of IgLON5 antibodies. In this case, early initiation of immunotherapy after antibody identification led to gradual improvement of neurological symptoms, possibly related to the decrease in IgLON5 antibody titer. After more than one year of follow-up, the patient's MMSE score was 28 points, and sleep disorder-related symptoms did not recur.

Conclusion

Anti-IgLON5 antibody-associated encephalopathy is a heterogeneous disorder characterized by a wide spectrum of clinical manifestations. The disease trajectory exhibits variable dynamics and may overlap with other neurological conditions. For patients with common clinical symptoms such as sleep disturbances, chronic progressive symptoms similar to Parkinson's disease or progressive bulbar palsy, memory impairment, prompt and precise diagnosis necessitates the detection of specific antibodies. The appropriate diagnostic strategy should encompass a thorough clinical evaluation, testing for anti-IgLON5 antibodies in both CSF and serum, as well as HLA genotyping. It is important to note that atypical clinical presentations may arise due to the antibody's activation of pathways that can elicit robust inflammatory responses in the patient.

This case report delineates an acute onset of anti-IgLON5 disease, characterized by meningeal enhancement and atypical clinical and MRI findings. Notable improvement was observed following immunotherapy. Given the rarity and complexity of this condition, the findings contribute to the broader understanding of this uncommon autoimmune disorder and facilitate its diagnosis.

Declarations

Abbreviations

IgLON5	Immunoglobulin-like cell adhesion molecule 5
CSF	Cerebrospinal fuid
MRI	Magnetic resonance imaging
HLA	Human leukocyte antigen
GCS	Glasgow Coma Scale
EBV	Epstein-Barr virus
MMSE	Mini-Mental State Examination
IVIG	Intravenous human immunoglobulin
TPE	Therapeutic plasma exchange
IgG	Immunoglobulin G

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

Supplementary Material 9

Supplementary Material 10

Supplementary Material 11

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Author contributions
Conceptualization: Huasheng Huang, Yizhi Wei. Data collection: Huasheng Huang, Yizhi Wei. Investigation: Jie Li. Writing – original draft: Jie Li. Writing – review & editing: Huasheng Huang, Jie Li. All authors have reviewed the data analysis process, writing of the manuscript, and approved the final article.

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Data availability
The principal data gathered during this study are included in this article. The datasets used during the current study are available from the corresponding author on reasonable request. Figure used in the study was original and made by the authors.

Declarations

Ethics approval and consent to participate
This study was was in accordance with the ethical standards of Liuzhou People's Hospital affiliated to Guangxi Medical University and with the Helsinki declaration. The patient provided written informed consent according to the Declaration of Helsinki.

Consent for publication
Patient gave written informed consent for their personal or clinical details and any identifying images to be published in this study.

Competing interests
The authors declare no competing interests.

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