Clinical Case Report

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Autoimmune encephalitis with anti-IgLON5 and anti-GABA$_B$-receptor antibodies

A case report

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Abstract

Rationale: Anti-IgLON5 disease is a complex neurological illness which is characterized by progressive sleep and movement disorders and defined by specific autoantibodies to IgLON5. We here describe the first case of a patient with coexisting anti-IgLON5 as well as anti-γ-aminobutyric acid B (GABA$_B$)-receptor antibodies and predominant clinical features of anti-IgLON5 disease.

Patient concerns: The patient initially presented with subacute symptoms of severe sleep disorder, gait stability, dysarthria, cognitive impairment, depressive episode and hallucinations.

Diagnoses: The patient was diagnosed with autoimmune encephalitis, based on clinical features and positive anti-IgLON5 antibodies in serum as well as in cerebrospinal fluid and anti-GABA$_B$-receptor antibodies in serum only.

Interventions: Initially, the patient was treated with high dosages of methylprednisolone and subsequently with plasmapheresis. Due to the lack of clinical improvement immunosuppressive treatment with intravenous cyclophosphamide was initiated.

Outcomes: Following the first year of cyclophosphamide treatment, neurological examination revealed an improvement in gait instability, visual and acoustic hallucinations and sleep disorder.

Lessons: The case report demonstrates that anti-IgLON5 and anti-GABA$_B$-receptor antibodies can coexist in the same patient whereas clinical leading symptoms are determined by those antibodies that were tested positive in cerebrospinal fluid.

Abbreviation: GABA$_B$ = γ-aminobutyric acid B.

Keywords: anti-GABA$_B$ receptor, anti-IgLON5, autoimmune encephalitis, cyclophosphamide, neurodegeneration, neuroinflammation, sleep disorder

1. Introduction

Anti-IgLON5 disease is a rare and enigmatic neurological disorder first described and characterized in 2014 by Sabater *et al*.[1] The disease-defining antibodies target a neuronal cell adhesion protein, whose function is still not well understood. Patients with anti-IgLON5 disease show histopathological features of a neurodegenerative disorder including tau phosphorylation and deposition in neurons. Often therapeutic response is limited.[2] Thus, it is still under debate whether anti-IgLON5 disease is an autoimmune disorder triggering secondary neurodegenerative events or a primarily neurodegenerative disease with associated specific antibodies being an accompanying phenomenon. The disease is mainly characterized by severe sleep disorder (e.g., parasomnia, insomnia, excessive daytime sleepiness, and sleep-disordered breathing), bulbar symptoms (e.g., dysphagia and dysarthria), and gait abnormalities (e.g., Pisa syndrome).[2,3] Patients typically show strong association with HLA-DRB1*10:01 and HLA-DQB1*05:01 haplotypes whereas manifestation of symptoms is heterogeneous and may also present in different severity and different combinations.

Anti-γ-aminobutyric acid B (GABA$_B$)-receptor encephalitis represents 5% of all known autoimmune encephalitis syndromes mostly presenting with limbic encephalitis including seizures, cognitive impairment, confusion, and personality changes.[4,5] In almost 50% of patients, anti-GABA$_B$ encephalitis is tumor associated, mostly with small-cell lung cancer.[6]

2. Case presentation

A 58-year-old male patient was initially admitted to a psychiatric hospital with a major depressive episode, fatigue, and affective flattening and later transferred to the neurological department for

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further diagnostic evaluation. He further complained about deterioration of his general state of health and weight loss of almost 26 kg in the last 9 months; no night sweat was reported. During the patient's stay in the psychiatric ward, he developed dysarthria and gait instability manifesting as a Pisa syndrome as well as apraxia and dysdiadochokinesis (see Supplemental Video 1, http://links.lww.com/MD/C988). Most prominent, the patient showed a severe sleep disorder with parasomnia exhibiting repeated episodes of complex motor behaviors (e.g., falling out of bed) and insomnia resulting in repetitive sleep attacks of almost 20 times a day. In addition, he complained about visual and acoustic hallucinations. His medical history revealed a long history of recurring depressive episodes with several inpatient treatments and 2 suicide attempts, borderline disorder, and long-term smoking (20 pack-years).

In the neuropsychological evaluation, the patient scored 27/30 on the Mini-Mental State/Examination and 19/30 on the Montreal Cognitive Assessment presenting a moderate cognitive impairment. In addition, he had a Self-rating Depression Scale score of 13/21 and Self-rating Anxiety Scale score of 15/21.

Cranial magnetic resonance imaging and electroencephalography revealed no abnormalities, especially no signs of limbic encephalitis or epileptiform discharges were found. In further laboratory testing, anti-IgLON5 antibodies were found positive in cerebrospinal fluid (titer 1:10) as well as serum (titer 1:320 and 1:1000 in a confirmation test), whereas anti-$GABA_B$-receptor autoantibodies were found positive in serum only (titer 1:100). Corroborating the hypothesis of anti-IgLON5 disease, we found the haplotypes HLA-DRB1*10:01 and HLA-DQB1*05:01, which is highly associated with anti-IgLON5 disease. The polysomnography showed reduced total sleep time, sleep efficacy, and increased sleep fragmentation characterized by predominant measurement of wake electroencephalography and with only few periods of sleep stage N1. Due to the massively reduced sleep time, no statement regarding a potential sleep-disordered breathing was possible. The patient did not agree to repeat the examination. Due to the association of anti-$GABA_B$-receptor autoantibodies with tumors, we further performed an 18F-fludeoxyglucose positron emission tomography/computed tomography, which revealed no signs of tumor.

The patient was then treated with methylprednisolone 1000 mg/d for 5 consecutive days without clinical improvement. Therefore, we initiated plasmapheresis as an escalation therapy followed by additional treatment with methylprednisolone 1 g/d for another 5 consecutive days. Despite repetitive cycles of plasma exchange and methylprednisolone treatment, disease symptoms rather deteriorated. We then decided to start immunosuppressive treatment with monthly intravenous pulses of cyclophosphamide (500 mg/m^2 body surface). Thereafter, disease symptoms, for example, gait instability, dysarthria, sleep disorder, and hallucinations, stabilized and improved. Interestingly, in the follow-up examination 16 months after 13 cycles of cyclophosphamide (cumulative dose of 11.7 g), the patient still complained about recurring visual and acoustic hallucinations, but the gait instability (Pisa syndrome) and sleep disorder including parasomnia and insomnia appeared to be significantly improved (see Supplemental Video 2, http://links.lww.com/MD/C989).

3. Discussion

Previous case reports already described the coexistence of anti-$GABA_B$-receptor and anticollapsin response-mediator protein 5 antibodies[7] or anti-$GABA_B$ receptor and anti-CRMP5/CV2 antibodies.[4] Here, we present a patient revealing anti-IgLON5 and anti-$GABA_B$-receptor antibodies. Interestingly, the clinical syndrome is clearly dominated by "classical" symptoms of anti-IgLON5 disease without distinct features of limbic encephalitis as it is known from anti-$GABA_B$-receptor-associated autoimmune encephalitis. Anti-IgLON5 encephalitis is a very rare and recently described neurological disorder that is mainly characterized by severe sleep disorder (e.g., parasomnia, insomnia, excessive daytime sleepiness, and sleep-disordered breathing), gait instability, and dysarthria,[8] which all were present in our patient. The patient described in this case report had a long psychiatric history of recurrent depressive episodes and was presently hospitalized due to a major depressive episode and personality changes. The patient also complained about recurrent visual and acoustic hallucinations that improved subsequently following cyclophosphamide therapy, but worsened 1 week before the next cycle. It is known that recurrent visual and acoustic hallucinations are part of the anti-IgLON5 syndrome.[9] Similarly to the previous reports,[2,8] initial immunotherapy with plasma exchange and methylprednisolone did not result in stabilization of disease progression. However, stringent immunosuppression with cyclophosphamide seems to have beneficial effects in an advanced disease stage supporting current reports describing beneficial effects of immunotherapy in cases of IgLON5 disease.[9]

In the presented patient, 2 antineuronal antibodies were found that are associated with distinct subtypes of autoimmune encephalitis. However, the clinical syndrome is dominated by anti-IgLON5 disease. As shown in *N*-methyl-D-aspartate receptor encephalitis, highly specific intrathecal antibodies to the GluN1 subunit are causative for the disease.[10] Against this, it is currently unclear if serum antibodies of either subclass (immunoglobulin (Ig)G, IgA, and IgM) that have been reported in a variety of clinical syndromes and even in healthy individuals have any clinical relevance.[11,12] As in our patient, only anti-IgLON5 antibodies have been detected in cerebrospinal fluid, this may be one underlying reason why the clinical syndrome is shifted toward anti-IgLON5 disease and does not show typical features of $GABA_B$-receptor encephalitis.

Clinical stabilization upon cyclophosphamide may point toward an autoimmune component in the etiology of the disease; however, the pathophysiological function of anti-IgLON5 antibodies remains to be investigated.[13]

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Author contributions

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