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Anti-leucine-rich glioma inactivated protein 1 encephalitis with sleep disturbance as the first symptom: a case report

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Abstract

BACKGROUND

Anti-leucine-rich glioma inactivated protein 1 (anti-LGI1) encephalitis is an infrequent type of autoimmune encephalitis (AE) characterized by acute or subacute cognitive and psychiatric disturbance, facio-brachial dystonic seizures (FBDSs), and hyponatremia. Anti-LGI1 AE has increasingly been considered a primary form of AE. Early identification and treatment of this disease are clearly very important.

CASE SUMMARY

Here, we report that a male patient developed severe anti-LGI1 encephalitis, which was initially misdiagnosed as a sleep disturbance. He was hospitalized for epileptic seizures and typical FBDSs half a month after he developed sleep disturbances. LGI1 antibodies were detected in his cerebrospinal fluid and serum (1:100 and 1:3.2, respectively), which led to the diagnosis of classic anti-LGI1 AE. No obvious abnormality was observed on brain computed tomography (CT) images. T2-weighted fluid-attenuated inversion recovery (FLAIR) and T2-weighted scans of brain magnetic resonance imaging (MRI) showed slightly elevated signals within the left basal ganglia area. No tumor was detected within the brain of this patient using MRI.

After hormone and antiepileptic drug treatment, the patient's symptoms improved significantly.

CONCLUSION

Anti-LGI1 antibody-associated encephalitis has characteristic clinical manifestations, such as cognitive impairment, psychiatric symptoms, seizures, sleep disorders, hyponatremia, and FBDSs. LGI1 antibodies are present in the serum and/or cerebrospinal fluid, but their production is sensitive to immunosuppressants, and this disease has a relatively good prognosis. In particular, we should be aware of the possibility of anti-LGI1 antibody-associated encephalitis in adolescents with sleep disorders to avoid missed diagnoses and misdiagnoses.

INTRODUCTION

In general, the phrase autoimmune encephalitis (AE) is defined as diseases caused by antigen-antibody reactions of the immune system to the central nervous system[1]. The main clinical manifestations of AE are acute or subacute epileptic seizures, facio-brachial dystonic seizures (FBDSs), cognitive disturbances, and mental disorders.

Sleep dysfunction in patients with AE has received little attention and is most likely neglected because clinicians pay more attention to neurological and psychiatric symptoms. Nevertheless, sleep disorders are very common in AE patients and often persist beyond the acute stage, which seriously affects patients' quality of life. All patterns of somnipathy can arise in AE patients due to the influence of the disease on an extensive number of brain networks participating in sleep initiation and regulation. Anti-IgLON5 and anti-N-methyl-d-aspartate (NMDA) receptor encephalitis are two representative diseases in which sleep disturbances are common and serious. Somnipathy varies according to the disease stage in anti-NMDA receptor encephalitis, and the core symptom in anti-IgLON5 disease is sleep disorders [2].

However, few reports described sleep disorders associated with anti-LGI1 antibody encephalitis. Anti-LGI1 antibody-associated encephalitis is a type of AE that is characterized by epilepsy, a recent memory decline, and mental and behavioral abnormalities as its main clinical manifestations. Since anti- LGI1 encephalitis is a recently identified disease, limited data are available on its clinical manifestation, especially in patients presenting with sleep disturbances as the initial symptom. Here, we report a patient who developed severe anti-LGI1 encephalitis, which was initially misdiagnosed as a sleep disorder. The patient was hospitalized for epileptic seizures and typical FBDSs half a month after he developed the sleep disturbance.

CASE PRESENTATION

Chief complaints

sleep disorders , sudden limb convulsions with unconsciousness

History of present illness

This patient initially visited the doctor because he suffered from suddenly persistent insomnia (with difficulties initiating and especially maintaining sleep). Dream enactment and somniloquy occurred during his sleep, and he felt fatigue and weakness after waking in the morning. The doctor prescribed some sleeping pills. No significant improvement was observed after taking the medicine for several days. Half a month later, his right hand twitched involuntarily in the evening before admission when he had his hair cut; this symptom lasted for approximately 3 s and was not given much attention. After waking the next morning, he had two other attacks with intervals of approximately half an hour, lasting approximately 3–5 s each. Then, secondary limb convulsions appeared as follows: flexion of both upper limbs, ankylosis of both lower limbs, unconsciousness, eyes turning up, crown closure, and mouth foaming, which lasted for approximately five minutes. Immediately, the patient's consciousness became lucid, and after waking, he could not recall the course of the disease and experienced slight dizziness and headache

History of past illness

He had previously been healthy.

Personal and family history

There is no history of familial genetic diseases.

Physical examination

The neurological examination showed no obvious abnormality.

Laboratory examinations

The white blood cell count ($11.23*10^9$ cells/L) and neutrophil percentage (89%) increased significantly in the full blood count. All biochemical indexes and thyroid function were normal or negative.

Cerebrospinal fluid (CSF): A routine CSF examination displayed acellular fluid. No bacterial growth or abnormal biochemistry was observed in the CSF. The opening pressure was not abnormal. CSF cytology showed that the percentage of leukocytes in multiple nuclei increased by 50% (reference value 0–6%), and the other indexes were normal.

Detection of autoimmune antibodies: LGI1 antibodies were examined and were positive in both the serum and cerebrospinal fluid (1:100 and 1:3.2, respectively), and other antibodies (contactin-associated protein 2 (CASPR2), N-methyl-D-aspartate receptor (NMDAR), glutamic acid decarboxylase (GAD65), GABA, and AMPA1) were negative (Fig. 1, Figure 2), which confirmed the diagnosis.

No abnormalities in hepatitis B surface antibody test results. Human immunodeficiency virus (HIV) antibodies and *Treponema pallidum*-specific antibodies were normal or negative.

Imaging examinations

A CT scan of the thorax showed inflammation of the right lower lobe of the lung. No abnormality was detected on the brain CT scan.

Brain magnetic resonance imaging (MRI) (Figure 3) results: An abnormal shadow signal was observed in the left basal ganglia area, which displayed a high signal in T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI and T2-weighted MRI.

FINAL DIAGNOSIS

Anti-leucine-rich glioma inactivated protein 1 (anti-LGI1) encephalitis

TREATMENT

Immunotherapy was initiated with dexamethasone, and a continuous intravenous infusion of sodium valproate was administered to control the seizures.

OUTCOME AND FOLLOW-UP

No major seizures occurred during hospitalization, but intermittent FBDSs persisted during the first several days after hospitalization. One week later, FBDSs did not appear. Two weeks later, the patient's symptoms improved significantly, and thus he was discharged and was told to gradually reduce the dose of prednisone after discharge. During hospitalization, the patient's sleep disturbances gradually decreased, and the patient's sleep completely returned to normal at discharge.

The patent was discharged with antiepileptic therapy and corticosteroid. He is followed up every three months.

DISCUSSION

The incidence and mortality rates of encephalitis are 8–18.45% [4–7]. The disease has been recognized by an increasing number of clinicians since the first case of teratoma-related anti-NMDA receptor encephalitis was reported in 2007[8].

Dalmau *et al* [9] were the first to report that anti-NMDAR encephalitis has a close relationship with teratoma in 2007. Lai *et al* [10] first discovered anti-AMPA receptor

encephalitis in 2009, and Lancaster *et al* [11] identified anti-GABABR encephalitis in 2010. Anti-LGI1 antibody encephalitis and anti-CASPR2 antibody encephalitis were first discovered by Lai *et al* [12] in 2010. Anti- LGI1 encephalitis is infrequently associated with tumors, and most patients recovered after treatment with steroids or other immunotherapies. [13].

A survey discovered that AE substantially affected the patients' quality of life[14]. The diagnosis of AE is very difficult due to its sophisticated clinical symptoms [15]. The key to the diagnosis of AE is a neuronal autoimmune antibody, and a close relationship has been observed between the difference in the antibody titer and its clinical course. [16].

The main manifestations of anti- LGI1 encephalitis are epilepsy, cognitive and mental disorders, hyponatremia, and sleep disorders, and explanations are provided below.

Epilepsy

Among the patients positive for LGI antibodies, twenty percent-forty percent[17] have FBDSs, which are short, frequent, and unconscious seizures, together with dystonia, simple upper limb spasm and contraction, and ipsilateral face twitch (not long, 3 s, several times a day). Some scholars [18] postulate that FBDSs might be dystonic. However, Irani *et al* [19] and other scholars proposed that FBDSs were a type of epileptic seizure.

Previous studies have discovered that ninety percent of patients have seizures that primarily present in the following three types: FBDS, focal to bilateral tonic–clonic seizure (FBTCS) and mesial temporal lobe epilepsy (MTLE)-like seizure [20-26]. In a recent study, patients with anti-LGI1 AE were divided into the following three groups according to the epilepsy symptomatology: FBDS alone (FBDS-only), epileptic seizures without FBDS [non-FBDS], and coexistence of FBDS and other seizures (FBDS+) [27]. Researchers found that FBDSs were significantly decreased and even vanished after treatment with oral steroids [28]. Basal ganglia lesions are present in patients with FBDSs [1].

FBDSs are the particular seizure type experienced by anti-LGI1 AE patients, and probably half of the patients experience FBDSs [20, 21, 22, 19, 29]. FBDSs are easy to identify and diagnose; however, EEG shows abnormalities during onset in only a few patients [19, 29]. The origin of FBDSs remains controversial. Cortical, subcortical, and cortical-subcortical origins have been shownby distinct studies[27, 30, 31]. A study on anti-LGI1 AE [18] concluded that anti-LGI1 antibody-associated encephalitis commonly damaged the hippocampus and basal ganglia, which was slightly different from a previous study that discovered that the motor cortex and hippocampus may be two main targets in anti-LGI1 AE [24, 20]. In addition, immunotherapy reduces epileptic seizures and prevents complications[32]. A study [33] reported high T2 and FLAIR signals in the bilateral temporal lobe and hippocampus on brain MRI [18]. This finding is consistent with the report that LGI1 is primarily expressed in the temporal cortex and hippocampus.

The seizure form experienced by this patient FBDS+, and the symptoms were obviously relieved after treatment with hormone and antiepileptic drugs, consistent with the characteristics of anti-LGI1 encephalitis.

Cognitive and mental impairment

Previous studies discovered that approximately ninety-five percent of patients suffered from cognitive dysfunctions. Majoie *et al* [34] discovered that eighty-nine percent of LE patients had dysmnesia. Malter *et al* [17] identified relationships between cognitive impairment and the disease course before immunotherapy.

The main manifestations of mental/behavioral disturbances are individual and behavioral abnormalities, such as prone to anger, anxiety, impulsive behavior, and hallucinations [35, 36]. Serum anti-LGI1 antibodies may remain detectable after full clinical recovery [37]. A similar mechanism[36] can be hypothesized in anti-LGI1 encephalitis because the LGI1-ADAM22-AMPAR interaction is proposed to influence long-term depression (LTD) [38, 39]. As LTD is also essential for spatial memory,

disruption of this process might explain the spatial disorientation observed in patients with anti-LGI1 encephalitis.

Hyponatraemia: As reported, hyponatraemia occurs in sixty percent of patients with LGI1 AE [21, 18]. The main reason was regarded as abnormal secretion of antidiuretic hormones, which will be correlated with simultaneous LGI1 expression in the hypothalamus and kidney.

4) Brain MRI: Most LE patients presented abnormal T2 and FLAIR signals in bilateral temporal lobe regions on brain MRI, and a small proportion of patients showed abnormal signals in one side of the hippocampus. Furthermore, the lesions often involve the temporal lobe and basal ganglia [40]. In some patients with FBDSs, high T1/T2 are detected signals on brain MRI [41] and high FDG-PET metabolism has been observed in the basal ganglia [19].

In our case, FLAIR and T2-weighted scans showed slightly elevated signals within the left basal ganglia area, consistent with the characteristics of anti-LGI1 encephalitis detected using MRI.

5) Sleep disturbances: Sleep disturbances are also common in patients with AE [42]. Sleep dysfunctions have also been described in association with various neuron-specific antibody biomarkers, including IgLON5, LGI1, CASPR2, NMDA receptor, and Ma2. There are four forms of sleep disorders: rapid eye movement sleep behavior disorder, hypersomnia, fragmented sleep, and sleep-disordered breathing. New sleep complaints (e.g., gasping and snoring) were reported by seventy-three percent of AE patients in one study [43].

LGI1 is a glycoprotein located in the synapse and primarily expressed in the neocortex and hippocampus [44]. A recent study of PSG revealed that sleep efficiency, total sleep time, N3 sleep and REM sleep decreased significantly in anti-LGI1 encephalitis patients [45]. Another study [46] demonstrated that sleep efficiency and total sleep time were obviously reduced in anti-LGI1 AE patients. An imbalanced sleep structure was discovered, showing ascended N1, reduced N3, REM components and an abnormal N2 structure. These findings were not related to nocturnal episodic events or

the presence of sleep hyperkinetic movements (HMs). Animal experiments have shown that LGI1 antibodies play a neurotoxic role, potentially mediated through the reduction in calcium currents and induction of apoptosis [47]. The LGI1 gene is widely expressed in the hypothalamus, including the ventromedial nucleus [48]. The ventromedial nucleus contains glycine/GABA neurons and receives direct synaptic input from glutamatergic neurons in the sublaterodorsal tegmental nucleus. Studies have shown that silencing this circuit may lead to REM sleep without atonia [49]. Antibodies binding to hypothalamic neurons may result in hypothalamic disturbances, likely leading to RBD and insomnia. Clinical and PSG outcomes improved after immunotherapy [50].

However, other authors [51, 52] found that the chief immunological targets of anti-LGI1 encephalitis are the motor cortex, limbic system, brainstem and striatum thalamus, consistent with the findings that LGI1 is broadly expressed in neurons and some axonal terminals throughout the central nervous system (CNS).

In this case, the manifestations of sleep disorders were persistent insomnia (with difficulties initiating and especially maintaining sleep), dream enactment and somniloquy, which lasted for half a month before the seizures began. Furthermore, sleep disorders responded poorly to general sleeping pills, and the symptoms were relieved rapidly after immunotherapy, consistent with the characteristics of sleep disorders in AE.

In conclusion, sleep disturbance, marked by symptoms including sleep fragmentation, dream enactment behaviors and ambiguous or total loss of physiological sleep rhythms, could be a visible and inherent characteristic of anti-LGI1 encephalitis.

Improving the detection of sleep disorders is conducive to the early detection of anti-LGI1 AE, especially in patients presenting with sleep disorders as the initial symptoms; this approach may prevent missed diagnoses and misdiagnoses. Additionally, this approach may allow patients to receive treatment as soon as possible and promote the early recovery of patients.

6) EEG: Usually, a specific change in EEG is not observed in patients with anti-LGI1 AE. The abnormal EEG for FBDSs is probably caused by a deeply located or highly localized epileptogenic zone [21, 23].

CONCLUSION

The case report illustrates the importance of antibody testing and early recognition of sleep disturbances in identifying this condition, which is often undiagnosed. Early recognition and initiation of therapy are important in the management of patients with anti-LGI1 AE and their prognosis and may both prevent perpetual neurological impairment and improve long-term outcomes.Unfortunately, polysomnography and FDG-PET were not completed due to the limitations of our hospital's facilities. In a future study, we will try to collect these data.

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