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Original Article

Sleep Structure Abnormality Associated with Cognitive Impairment in Lgi-1 Positive Autoimmune Encephalitis Patient: A Long-Term Follow-Up Case Study

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Abstract:

We reported a long-term follow-up anti-LGi-1 positive autoimmune encephalitis (LGi-1 AE) case that presented special sleep disorder associated with cognitive impairment during exacerbating and recovery stage that was not reported previously.

Methods: A LGi-1 AE patient underwent neuropsychological and sleep assessment including polysomnography in both exacerbating and fifteen months recovery stages.

Results: At exacerbating stage, neuropsychological evaluation indicated a moderate cognitive impairment. Polysomnography results showed severe sleep fragmentation、sleep efficiency decrease, and complete loss of N3 and REM sleep. At recovery stage after fifteen months, neuropsychological evaluation revealed improved cognitive function while mild memory impairment was still observed. Polysomnography results showed improvement of sleep fragmentation, normal sleep efficiency, and normal REM sleep. N3 sleep remained shorter than that of healthy control. These results indicated that the sleep structure abnormality was synchronized with cognitive impairment. Even in recovery stage, the shortened N3 sleep was coexisted with mild memory impairment.

Conclusion: In our LGi-1 AE patient, main sleep structure abnormality included sleep fragmentation, and loss of N3 and REM sleep may leaded to cognitive impairment. Bilateral lesions at the hippocampus might lead to both the sleep structure abnormalities and the cognitive impairment in our case.

Keywords : LGi-1; Sleep Structure; Cognitive impairment; Autoimmune Encephalitis; Polysomnography.

1. Introduction

Autoimmune encephalitis (AE) is commonly characterized by subacute and progressive dementia and epileptic fit. Recently, there has been growing interest in sleep disorders associated with AE. Sleep disorders were reported in AE patients, including those with different types of antibodies, such as VGKC, NMDA, IgLON5 and Ma. These sleep disorders mainly include rapid eye movement sleep behavior disorder (RBD), daytime somnia, sleep disordered breathing, and insomnia [1-5]. However, most of the previous studies on AE related sleep disorders were carried out at several months after treatment, and the effect of medications on sleep cannot be excluded. Additionally, these studies lacked simultaneous neuropsychological assessment and long-term follow-up. Therefore, the natural appearance, outcome, and possible relationship between sleep disorders and cognitive function remain unclear. In this study,we evaluated the sleep disorders during both the exacerbating and recovery stage after a 15-month long-term follow-up in a patient with anti-LGi-1 positive autoimmune encephalitis (LGi-1 AE), along with simultaneous cognitive function and psychological evaluation. We excluded the effect of medicine and other possible factors to accurately display the natural appearance, related factors, and outcome of sleep disorders in the LGi-1 AE patient. Furthermore, we try to explore the possible pathological mechanism of LGi-1 AE sleep disorders associated with cognitive impairment. The study was approved by the Ethics Committee in Jilin Central General Hospital and was conducted according to the principles of the Declaration of Helsinki.

2. Case

A 68-year-old male patient was hospitalized for memory deficits, irritability, overeating for two months, and epileptic fit for one month. The patient had a history of coronary disease for 6 years as well as had not any sleep disorders and cognitive impairment. Physical examination showed no abnormality. The patient underwent laboratory tests and imaging examinations, including standard biochemistry, tumor markers, cerebrospinal fluid (CSF) test, autoimmune encephalitis-related antibodies, other neuronal surface- or synaptic protein-related antibodies, classical paratuberculosis antibodies, and brain MRI. The following positive results were found: Anti-LGI1 antibody was detected in both serum (1:32) and CSF (1:10). The brain MRI showed high signal intensity in the bilateral mesial temporal lobe, including the hippocampus, on FLAIR and DWI sequences.

At exacerbating stage, after excluding the possible effects of medications and other factors, the patient accepted neuropsychological and sleep assessment. The neuropsychological assessment revealed cognitive impairment: Mini-Mental State Examination (MMSE) score was 22 (normal value: ≥ 27 points), Montreal Cognitive Assessment (MoCA) score was 19 (normal value: > 26 points), indicating impairment of visual-spatial, attention, language, abstraction, and memory deficits. The patient scored 9 on the Hamilton Anxiety Scale (HAMA) (normal value: < 7 points) and 6 on the Hamilton Depression Scale (HAMD) (normal value: < 7 points).

The sleep assessment included current sleep symptom、sleep questionnaires and overnight polysomnography (PSG) exam. Excepting mild daytime sleepiness, no other sleep symptom were presented such as daytime cataplexy, sleep insertion, snoring, apnea, dream enactment behavior and uncomfortable urge to move the legs or limb movements during sleep. The sleep questionnaires results included: Epworth Sleepiness Scale (ESS): 13 points (normal value: ≦ 7 points), presenting a drowsiness in quiet environment during the daytime; Insomnia Severity Index (ISI) : 5 points (normal value: ≦ 7 points), the main complain was early awakening

and poor sleep maintaining.

PSG exam was performed and scored by a board-certified sleep medicine physician in accordance with the AASM Manual for the Scoring of Sleep and Associated Events (Versions 2.6). PSG exam results (Fig1 and Table1) showed prolonged sleep onset latency to 39 mins, severe sleep fragmentation, and shorten total sleep time (TST) to 265 mins. The sleep efficiency decreased to 61.8% [6]. Especially N3 sleep and REM sleep were completely absence. The negative results included: Apnea Hyponea Index (AHI): 4.5. Limb discomfort before bedtime and behavioral abnormalities during sleep including shouting, abnormal limb movements, dream enactment behavior, were not existed.

Tab.1 Sleep stages time in PSG.

	Acute stage		Recovery stage		Normal contral *	
	min	%SPT	min	%SPT	min	%SPT
Sleep period time	429.0		479.5		462	
Sleep onset latency	39.0		13.5		16.2	
Total sleep time	265.0		404.5		378.3	
NREM sleep	265.0	61.8	335.5	69.9		69.4
N1 sleep	21.5	5.0	29.0	6.0		10.3
N2 sleep	243.5	56.8	280.5	58.5		44.2
N3 sleep	0.0	0.0	26.0	5.4		14.9
REM sleep	0.0	0.0	69.0	14.4		10.3
Sleep efficiency		61.8		84.3		79.7

* Normal contral data from the report of Mitterling[6]

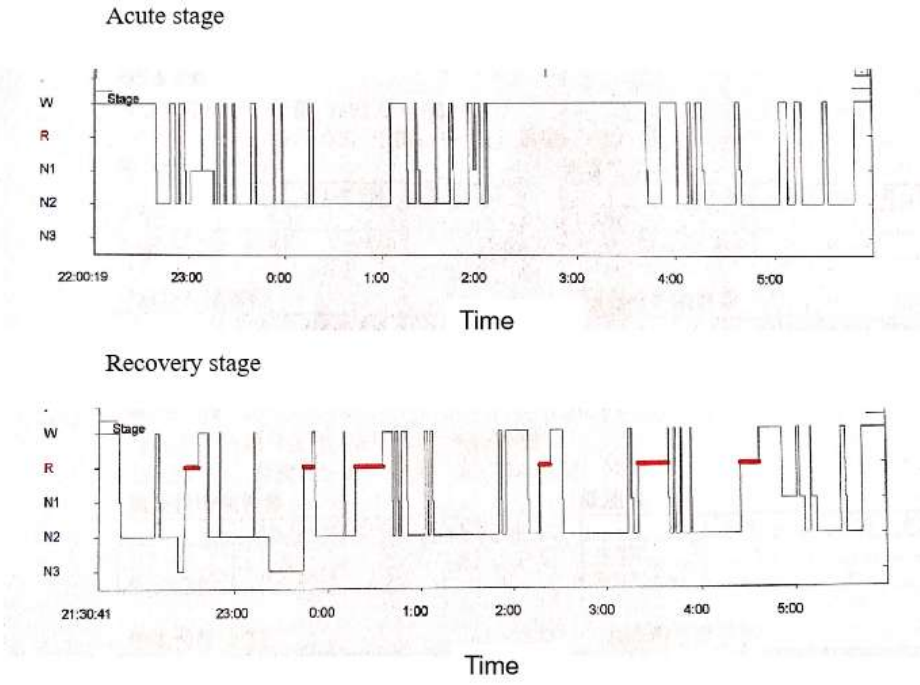

Fig.1 sleep structure chart in PSG.

W : wake, R: rapid-eye-movement sleep, N1: stage I sleep, N2: stage II sleep, N3: stage III sleep.

The patient was diagnosed with LGi-1 AE and treated with intravenous immunoglobulin and methylprednisolone, which resulted in gradual improvement of symptoms.

At recovery stage after fifteen months of illness onset, the patient without any medication, reported that no recurrence of symptoms, daily life and social activities were normal. He was satisfactory with his sleep, and denied any discomfort and symptoms related to sleep. Neuropsychological assessment was performed again, the results showed MMSE: 30 points ; MocA:26 points, revealed mild memory deficits; HAMA score: 7 points and HAMD:4 points (no scored in the sleep option).

Sleep assessment results showed ESS: 12 points, indicated daytime drowsiness; ISI value: 0 points. PSG exam results (Table1 and Fig1) showed normal TST and sleep onset latency, and improvement sleep fragmentation and sleep efficiency, especially disappeared N3 sleep and REM sleep at exacerbating stage were recovered: percentage of N3 sleep was 5.1% (26 mins) as well as REM sleep was 13.6% (69 mins). However, N3 sleep remained shorter than that of in same age healthy control [6]. AHI was 10.5. PLM and REM sleep dystonia were not found. Limb discomfort before bedtime, dream enactment behavior, uncomfortable urge to move the legs or limb movements during sleep were not existed.

3. Discussion

The findings of this study add to the growing body of literature suggesting that sleep disturbance is a significant feature of LGi-1 AE [1-5]. The findings of this study point out an interesting contradiction between subjective sleep assessments and objective PSG results, which may be associated with cognitive impairment in patients with AE. The study highlights the importance of conducting a comprehensive sleep evaluation included standardized sleep questionnaire evaluation and PSG in patients with AE to detect and diagnose any sleep disorders.

Sleep disturbance in our case was mainly characterized by abnormal sleep structure represented by severe N3 and REM sleep loss and fragmentation of sleep in exacerbating stage, . Through long-term follow-up, it was found that these abnormalities of sleep structure and cognitive impairment have synchronously improved. Even in the recovery period, the mild shortened N3 sleep and mild memory impairment coexisted. Recently Margaret S et al. observed 19 patients with various antibody-related limbic encephalitis including Ma, Hu, NMDA, LGI1, etc. [1], PSG results showed that the total sleep time, N3 and REM sleep of these patients were significantly shortened, even 1 case of NMDA and 1 case of LGI1-positive AE had a lack of N3 and REM sleep throughout the night. It is basically consistent with the results of our study. Indeed, there is a growing body of evidence suggesting the crucial role of N3 sleep in cognitive function, including memory and attention [7][8]. Similarly, a large number of experiments have confirmed that REM sleep plays a crucial role in the formation and consolidation of memory by activating nerve cells in the hippocampus, and deprivation of REM sleep will affect the formation and expression of memory and emotion[9][10].The abnormal sleep structure observed in AE patients, particularly the loss and fragmentation of N3 and REM sleep, may contribute to cognitive impairment in both the exacerbating stage and recovery stage of AE. These study suggested that abnormal sleep structure may be an unknown important pathogenesis resulted in cognitive impairment in AE patient. These findings suggest that correcting these sleep abnormalities could be a potential new treatment strategy for cognitive impairment in AE patients. However, more clinical studies are

needed to further explore this possibility and confirm its effectiveness.

The pathogenesis of sleep disturbance in AE is currently unclear. In this study, psychological evaluation did not show anxiety or depression as a factor. Previous studies have reported daytime sleepiness, hypersomnia, abnormal sleep structure, and REM sleep behavior disorder (RBD) [1-5]. RBD is common in neurodegenerative diseases[11], but neither AE patients in previous studies nor this patient had evidence of those diseases. It is believed that RBD in AE may be caused by damage to brainstem structures [12], but there is no evidence of such damage in these patients. VGKC antibodies may have a direct effect on the brainstem, but some researchers believe that dysfunction in the neural pathways projecting from the limbic system to the brainstem may be related to RBD[13]. The hypothalamus is an important lesion in limbic encephalitis[14][15], and recent studies suggest that impairment of the lhx6 neural pathway between a special GABA neural nucleus in the ventral zona incerta and the lateral nucleus of the hypothalamus may be involved in sleep disturbance in patients with LGi-1 AE[16-18]. This impairment may lead to a decrease in arousal level, causing hypersomnia, and block the conversion of NREM to REM sleep, resulting in the reduction or absence of REM sleep. Impaired regulation of the REM sleep or abnormal conversion of NREM and REM may also cause other complex sleep problems. Therefore the lesion in hypothalamus may be an important pathogenesis of in AE resulted in both sleep structure abnormality and cognitive impairment in AE patient.

4. Conclusion

In the LGi-1 AE patient, sleep disorders are exist in both exacerbating stage and recovery stage. Sleep assessment scales and PSG exam are indispensable for detecting sleep disturbances in AE patients. Sleep structure abnormalities such as sleep fragmentation and lose in N3 sleep and REM sleep may contribute to cognitive impairments. The hypothalamus and other limbic system lesions are believed to be responsible for both sleep structure abnormality and cognitive impairment. Understanding the underlying mechanisms will be beneficial to treatments for both sleep disorders and cognitive impairments in autoimmune encephalitis patients.

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