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Autonomic Dysfunction and Sleep Disorder in 35 Autoimmune Encephalitis

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ABSTRACT

Introduction: Considering that sleep disorders have garnered limited attention in patients with Autoimmune Encephalitis, often eclipsed by other prevailing neurological and psychiatric symptoms within this subgroup, identifying and addressing underlying sleep disturbances could alleviate AE-related complications and improve long-term outcomes. Consequently, the present study aims to ascertain the prevalence of sleep disorders and autonomic dysfunction in individuals grappling with autoimmune encephalitis within the confines of Isfahan City.

Methods: This descriptive–analytical study initially identified 50 autoimmune encephalitis patients. Fifteen patients were excluded due to loss to follow-up secondary to relocation or death. Consequently, a total of 35 patients who presented to neurology clinics in Isfahan between March 2023 and August 2024 were ultimately enrolled in the study. To measure the Sleep status, the Pittsburgh Sleep Quality Index were used. Data were analyzed using SPSS software (version 16). Statistical analyses were conducted employing the chi-square test and independent samples *t*-test. A p-value of less than 0.05 was considered statistically significant.

Results: The results indicated that sleep disorders and autonomic dysfunction were observed in 65.7% and 62.9% of patients, respectively, with no significant correlation between clinical symptoms and EEG findings. Furthermore, there was no significant association between these findings and MRI results, except for a noteworthy difference between sleep disorders and normal MRI findings ($P = 0.012 < 0.05$).

There was no statistically significant association between normal versus abnormal EEG findings and the signs and symptoms of autonomic dysfunction ($P = 0.783$). Similarly, no significant association was observed between abnormal MRI findings and autonomic dysfunction ($P > 0.05$).

In addition, no statistically significant relationship was found between normal versus abnormal EEG findings and sleep disturbances ($P = 0.710$), nor between abnormal MRI findings and sleep disturbances ($P > 0.05$).

Seventeen patients (48.57%) presented with both sleep disturbances and autonomic dysfunction concurrently. A significant association was observed between sleep and autonomic disturbances and antibody type in patients with autoimmune encephalitis ($P < 0.05$), with seronegative and anti-NMDA antibody–positive patients more frequently affected than those with other antibody types.

Conclusion: The findings indicate that the prevalence of sleep and autonomic disturbances in the autoimmune encephalitis patients is higher than that observed in the general population and is not necessarily associated with structurally detectable lesions on conventional imaging.

1. Introduction

Autoimmune encephalitis (AE) stands as an inflammatory brain disorder characterized by the emergence of psychiatric symptoms, cognitive impairment, and focal neurological deficits or seizures [1]. While clinical observations typically encompass cerebrospinal fluid (CSF) pleocytosis and distinct MRI findings, instances lacking overt signs of inflammation have progressively emerged within the clinical domain [2]. This condition can exhibit neurological symptoms, including memory deterioration, seizures, psychosis, and aberrant movements [3].

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In recent times, sleep disturbances have surfaced as a frequently cited occurrence among these patients, materializing as excessive daytime sleepiness, sleep-related breathing disorders, sleep parasomnias coupled with rapid eye movement (REM) behavior disorder, or narcolepsy [4].

Within distinct subcategories of AE, particularly AE associated with anti-IgLON5 antibodies, sleep-related complaints have been mentioned in almost 75% of patients [5].

In light of the critical and extensive influence sleep bears on human immunity and the indications from numerous animal and human studies pointing towards the potential augmentation of susceptibility to infections due to inadequate sleep, immune disruptions stemming from sleep deprivation may not be confined solely to a compromised response against pathogens; instead, they might also encompass a breakdown in immune tolerance [6]. Consequently, this breakdown could contribute to the genesis of autoimmune diseases. Thus, the interconnection between sleep disorders and autoimmune diseases exists as a two-way street, where each influences the other [7].

The autonomic nervous system is designed to maintain physiologic homeostasis [8]. Its widespread connections make it vulnerable to disruption by many disease processes including primary etiologies such as Parkinson's disease, multiple system atrophy, dementia with Lewy bodies, and pure autonomic failure and secondary etiologies such as diabetes mellitus, amyloidosis, and immune-mediated illnesses [9]. The result is numerous symptoms involving the cardiovascular, gastrointestinal, and urogenital systems. Patients with autonomic dysfunction (AUD) often have peripheral and/or cardiac denervation leading to impairment of the baroreflex, which is known to play a major role in determining hemodynamic outcome during orthostatic stress and low cardiac output states [10].

Certain studies posit that untreated sleep disorders might intensify this neurological disorder's clinical symptoms and pathological progression [11,12]. Furthermore, these disorders could cast a negative shadow over acute patient care, exacerbating autonomic instability, distorting cognitive function, and imperiling patients' overall quality of life [13].

Although clinical observations have identified various signs in AE, there is limited information regarding the co-occurrence of sleep and autonomic disturbances in these patients. A systematic investigation and identification of existing gaps could have significant clinical implications, contributing to a better understanding of these disorders and improving patient management.

On the other hand, autonomic dysfunction plays a critical role in regulating involuntary bodily functions such as heart rate, blood pressure, respiration, and body temperature. The presence of such dysfunction indicates disease exacerbation; therefore, early recognition of these signs allows physicians to implement more proactive therapeutic interventions. Additionally, alongside immunotherapy, pharmacological treatments can be administered concurrently to improve sleep quality.

On the other hand, understanding EEG and MRI findings related to sleep and autonomic disturbances can provide a broader perspective for patient management. The primary aim of this study was to determine the prevalence of sleep and autonomic disorders in patients with AE and to test the hypothesis that these disturbances are significantly associated with clinical features, EEG patterns, and MRI findings.

2. Methods

This descriptive–analytical study was conducted on 50 patients with autoimmune encephalitis, including both new and previously diagnosed cases, who attended the neurology clinics of Isfahan University of Medical Sciences between March 2023 and August 2024.

The study sample was selected through a census approach. 35 patients with autoimmune encephalitis were included in the study ultimately.

Fifteen patients were excluded from the study for various reasons, including poor general health, mortality, lack of consent to participate, relocation to another province or uncertain disease diagnosis upon reevaluation.

Diagnosis of autoimmune encephalitis confirmed by expert neurologist according to clinical presentation and MRI findings and especially the positive titration of antibody in CSF and serum. Informed consent was taken and all the necessary information regarding the study was disclosed to the patient and their families. The questionnaire survey was conducted anonymously to protect privacy.

The inclusion criteria for the study comprised patients who were diagnosed with AE based on clinical examinations, laboratory reports, EEG and MRI findings, and a definitive diagnosis by the treating physician. In fact, according to the Graus criteria (2016) [14], they were considered probable cases of autoimmune encephalitis. Additionally, all participants provided informed consent to take part in the study.

Exclusion criteria included patients with pre-existing sleep disorders, severe cognitive impairment, or diagnosed psychiatric conditions; chronic use of psychoactive or sedative medications, beta-agonists, or corticosteroids; autonomic nervous system dysfunction secondary to conditions such as diabetes, Parkinson's disease, or malignancies (e.g., lung SCC, breast cancer); and internal diseases including obstructive sleep apnea, heart failure, or renal failure.

A complete checklist including demographic features and disease characteristics was completed by the researchers using participants' files and an interview. To measure the Sleep status, the Pittsburgh Sleep Quality Index (PSQI) were used. It includes 9 questions devoted to investigate the respondents' sleep quality, required time to sleep, sleep duration, amount of useful sleep, sleep disorders, sleeping pills intake, and impact of insomnia on daily activities. The minimum and maximum scores for each item vary from 0 (no problem) to 3 (sever problem). The scores for different items were summed up to obtain a total score (0-21). The higher scores showed poorer sleep quality (Buysse et al., 1989).

Scores ranging from 0 to 7 indicated normal sleep, 8 to 14 showed mild sleep disturbance, 15 to 21 suggested moderate sleep disturbance, and scores above 22 indicated severe sleep disturbance.

Its reliability and validity has been confirmed in several studies (Cronbach's alpha = 0.83).

For detection of autonomic dysfunction, a complete neurological examination including size of pupil, heart rate, Blood pressure, gastrointestinal and Genitourinary autonomic symptoms was performed.

In this study, following clinical examination, the COMPASS-31 scale [15] was used to assess autonomic dysfunction. This scale is a 31-item patient-reported questionnaire evaluating six domains: orthostatic intolerance (10 points), vasomotor function (6 points), secretomotor function (7 points), gastrointestinal function (28 points), bladder function (9 points), and pupillomotor function (15 points). The total score ranges from 0 to 100, with higher scores indicating more severe neuropathic symptoms (0 = no symptoms, 100 = maximum symptom severity). Scores of 0–10 indicated normal or minimal autonomic symptoms, 11–30 indicated mild autonomic dysfunction, 31–50 indicated moderate dysfunction, and scores above 50 indicated severe autonomic dysfunction.

This study was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1401.009) and was conducted in accordance with the principles of the Helsinki declaration. The objectives of the study were explained to all participants, and written informed consent was obtained from those who agreed to participate.

All statistical analyses were performed using SPSS version 16.0. A p-value of <0.05 was considered statistically significant. Descriptive statistics were reported as mean ± standard deviation for continuous variables, and as frequency and percentage for categorical variables. Data analysis included *t*-test and X^2 (Chi-Square Test).

3. Results

We studied 35 definite Autoimmune encephalitis patients (54.3 %

male, n = 19; 45.7% female, n = 16), the age of whom was between 15 and 76 years (mean = 50.08 ± 17.47). The respective demographic and clinical characteristics of each Autoimmune encephalitis patients with Autonomic dysfunction are depicted in Table 1.

Seventeen patients (48.6%) had both sleep disturbances and autonomic dysfunction. Ten patients (28.6%) had severe sleep disturbances, and thirteen patients (37.1%) had severe autonomic dysfunction.

A significant association was observed between sleep and autonomic disturbances and antibody type in patients with autoimmune encephalitis ($P < 0.05$), with seronegative and anti-NMDA antibody–positive patients more frequently affected than those with other antibody types.

The most common finding of autonomic disorders was hypertension and the most common finding of sleep disorders was Insomnia (Table 2).

The respective EEG and MRI findings of each Autoimmune encephalitis patients with Autonomic dysfunction and sleep disorders are depicted in Table 3. The results indicated a statistically significant association between normal MRI findings and the absence of sleep disturbances ($P < 0.05$).

Table 2
Autonomic dysfunction and sleep disorder.

Autonomic Dysfunction	n (%)	Sleep Disorder	n (%)
Hypertension	12 (33.33)	**Hypersomnia**	4 (14.8)
Hypotension	0	**Insomnia**	12 (44.5)
Tachycardia	3 (8.33)	**Sleep Apnea**	4 (14.8)
Bradycardia	2 (5.56)	**Restless Legs Syndrome**	1 (3.7)
Hyperhidrosis	7 (19.44)	**Nightmare**	3 (11.1)
Anhidrosis	1 (2.78)	**REM Sleep Behavior Disorder**	2 (7.4)
Mydriasis	2 (5.56)	**Periodic Limb Movement**	1 (3.7)
Miosis	0	**No Symptoms**	12 (34.4)
Diarrhea	1 (2.78)	**Single Symptoms**	19 (54.3)
Constipation	8 (22.22)	**Multiple Symptoms**	4 (11.4)
No Symptoms	13 (37.1)		
Single Symptoms	13 (37.1)		
Multiple Symptoms	9 (25.7)		

4. Discussion

Autoimmune encephalitis encompasses a group of disorders wherein the host's immune system targets self-antigens expressed in the central nervous system [16]. Unlike paraneoplastic encephalitis, which involves a T-cell-mediated response, antibodies in autoimmune encephalitis are inherently pathogenic [17]. They induce inflammation by targeting specific neural proteins, including synaptic proteins, ion channels, and intracellular receptors. Structural changes occur when these antibodies bind to these target proteins, leading to an inflammatory response [18, 19].

Another category of diseases in which sleep disorders have been recently reported is autoimmune neurological disorders, such as autoimmune encephalitis, which can manifest with various neurological symptoms, including memory loss, seizures, psychiatric disturbances, and abnormal movements [20].

The objective of the present study was to determine the prevalence of sleep and Autonomic dysfunction in patients with autoimmune encephalitis. The results indicated that sleep disorders and autonomic dysfunction were observed in 65.7% and 62.9% of patients, respectively, with no significant correlation between clinical symptoms and EEG findings. Seventeen patients (48.57%) presented with both sleep disturbances and autonomic dysfunction concurrently. Furthermore, there was no significant association between these findings and MRI results, except for a noteworthy difference between sleep disorders and normal MRI findings. Patients without sleep disorders had significantly normal MRI findings. In fact, patients without sleep disturbances had

Table 1
Demographic and clinical characteristics.

Variable	Total	Autonomic Dysfunction 22 (62.9)	Non- Autonomic Dysfunction 13 (37.1)	*P value*	Sleep Disorder 23 (65.7)	Non- Sleep Disorder 12 (34.3)	*P value*
Gender, (M/F), n (%)	(19 (54.3)/16 (45.7))	13 (59.1)/9 (40.9)	6 (46.2)/7 (53.8)	0.458	13 (56.5)/10 (43.5)	6 (50)/6 (50)	0.713
Age, year, mean±SD	50.08 ± 17.47	53.40 ± 16.84	44.46 ± 17.74	0.146	51.41 ± 15.29	49.39 ± 18.8	0.750
Type of Antibody, n (%)							
Seronegative	14 (40)	12 (54.5)	2 (15.4)	0.016	9 (39.1)	5 (41.8)	0.013
NMDA	14 (40)	9 (41)	5 (38.5)		13 (56.5)	1 (8.3)	
GABA B	3 (8.5)	0	3 (23)		0	3 (25)	
GABA A	2 (5.7)	0	2 (15.4)		1 (4.3)	1 (8.3)	
ZiCK 4	1 (2.9)	1 (4.5)	0		0	1 (8.3)	
GAD65	1 (2.9)	0	1 (7.7)		0	1 (8.3)	
Initial Signs and Symptoms of Autoimmune Encephalitis, n (%)							
Seizures	7 (20)	5 (22.7)	2 (15.4)	0.948	4 (17.4)	3 (25)	0.971
Impaired Memory	8 (22.9)	5 (22.7)	3 (23.1)		6 (26.1)	2 (16.7)	
Behavioral Changes	7 (20)	5 (22.7)	2 (15.4)		5 (21.7)	2 (16.7)	
Weakness	3 (8.5)	2 (9.2)	1 (7.7)		2 (8.7)	1 (8.3)	
Imbalance	8 (22.9)	4 (18.2)	4 (30.7)		5 (21.7)	3 (25)	
Loss of Consciousness	2 (5.7)	1 (4.5)	1 (7.7)		1 (4.4)	1 (8.3)	
Duration of the Disease, months, mean±SD	26.34 ± 12.34	-	-	-	-	-	-
Immunotherapy, yes, n (%)	28 (80)	-	-	-	-	-	-
SLD, mean (95 % CI)	39 (28.10-49.94)	58.4 (47.77-69.03)	6.23 (5.20-7.25)	-	-	-	-
Normal Sleep	-	-		-	12 (34.3)		-
Mild SLD	-	-		-	5 (14.3)		-
Moderate SLD	-	-		-	8 (22.8)		-
Severe SLD	-	-		-	10 (28.6)		-
AD, mean (95 % CI)	13.88 (10.95-16.81)	-	-	-	19 (16.59-21.4)	4 (2.82-5.33)	
Normal or Minimal AD	-	13 (37.1)		-	-		-
Mild AD	-	2 (5.8)		-	-		-
Moderate AD	-	7 (20)		-	-		-
Severe AD	-	13 (37.1)		-	-		-

n: number, F: Female, M: Male, SD: Standard Deviation, CI: Confidence Interval for Mean, SLD: Sleep Disorder, AD: Autonomic Dysfunction.

Table 3
EEG and MRI findings with or without autonomic dysfunction and sleep disorder.

Variable		Total * (n = 35)	Autonomic Dysfunction 22 (62.9)	Non- Autonomic Dysfunction 13 (37.1)	*P value*	Sleep Disorder 23 (65.7)	Non- Sleep Disorder 12 (34.3)	*P value*
EEG Findings, n (%)								
Normal EEG		3 (8.6)	2 (9.1)	1 (7.7)	0.886	2 (8.7)	1 (8.3)	0.971
Abnormal EEG	Generalized Slow Waves	19 (54.3)	11 (50)	8 (61.5)	0.508	13 (56.5)	6 (50)	0.713
	Generalized Spike	9 (25.7)	6 (27.3)	3 (23.1)	0.784	7 (30.4)	2 (16.7)	0.376
	Focal Spike	7 (20)	5 (22.7)	2 (15.4)	0.600	6 (26.1)	1 (8.3)	0.231
	Temporal Slow Waves	6 (17)	4 (18.2)	2 (15.4)	0.832	2 (8.7)	4 (33.3)	0.066
	Frontal Slow Waves	4 (11.4)	2 (9.1)	2 (15.4)	0.572	1 (4.3)	3 (25)	0.068
	Delta Brush	1 (2.8)	1 (4.5)	0	0.435	1 (4.3)	0	0.464
MRI Findings, n (%)								
Normal Brain MRI		3 (8.6)	2 (66.7)	1 (33.3)	0.886	0	3 (25)	0.012
Abnormal Brain MRI	White Matter	8 (22.8)	5 (62.5)	3 (37.5)	0.981	6 (26)	2 (16.7)	0.529
	Juxtacortical	4 (11.4)	1 (25)	3 (75)	0.096	1 (4.3)	3 (25)	0.068
	Menangeal Enhancement	1 (2.8)	0	1 (100)	0.187	0	1 (8.3)	0.160
	Generalized Atrophy	9 (25.7)	7 (77.8)	2 (22.2)	0.282	7 (30.4)	2 (16.7)	0.376
	Basal Ganglia	5 (14.3)	2 (40)	3 (60)	0.235	3 (13)	2 (16.7)	0.771
	Unilateral/Bilateral Temporal	3 (8.6)/5 (14.3)	7 (87.5)	1 (12.5)	0.101	7 (30.4)	1 (8.3)	0.139
	Cerebellum	4 (11.4)	3 (75)	1 (25)	0.593	3 (13)	1 (8.3)	0.678
	Brainstem	2 (5.7)	2 (100)	0	0.058	1 (4.3)	1 (8.3)	0.630
	Insula	2 (5.7)	0	2 (100)	0.263	2 (8.7)	0	0.293
	Cortical	4 (11.4)	1 (25)	3 (75)	0.096	2 (8.7)	2 (16.7)	0.482

n: number, * A
mong the 35 patients with AE, 49 EEG findings and 50 MRI findings were identified.

significantly more normal MRI findings.

A significant association was observed between sleep and autonomic disturbances and antibody type in patients with autoimmune encephalitis ($P < 0.05$), with seronegative and anti-NMDA antibody–positive patients more frequently affected than those with other antibody types.

Studies by Blattner (2019) [5], and Muñoz-Lopetegi (2020) [21] have reported sleep disorders in patients with autoimmune encephalitis, including conditions like hypersomnia, rapid eye movement sleep behavior disorder (RBD), sleep-related breathing disorders, non-rapid eye movement (NREM) parasomnias, or narcolepsy. Sleep problems can persist even beyond the acute phase of autoimmune encephalitis.

The sleep disorder and autonomic dysfunction are important in beginning and the course of autoimmune encephalitis. Anti-IgLON5 encephalitis and anti-NMDA receptor encephalitis represent two conditions in which sleep disturbances are particularly prominent [21]. In the present study, a statistically significant association was also observed between antibody type and sleep disturbances.

Sleep and wakefulness disorders can impair daily functioning and have a detrimental impact on health and lifespan [22]. In this study, more than 60% of patients with autoimmune encephalitis experienced sleep and autonomic disturbances.

Sufficient sleep is essential for maintaining daily functioning, prompting numerous studies on sleep disorders in various populations [23]. These studies have revealed that the global prevalence of sleep disorders is nearly 36% [24]. Sleep disorders were estimated to affect 32% of the general population, 36% of healthcare workers, and a striking 75% of COVID-19 patients [25].

As demonstrated, the prevalence of sleep disturbances among patients with autoimmune encephalitis is higher than the general population and exceeds the global prevalence of these disorders.

The long-term cumulative effects of sleep deficiency and sleep disorders result in various adverse health consequences, including an increased risk of hypertension, diabetes, obesity, depression, heart attacks, and related strokes [26].

Blattner (2019) [5] conducted a study in Washington involving 26 individuals with an average age of 53 years (ranging from 18 to 83). Autoantibodies against intracellular antigens, including Ma and Hu antibodies, were identified in 23% of the patients, while antibodies against cell surface neuronal antigens, such as NMDAR and LGI1, were found in 77%. Sleep complaints were reported by 73% of the patients in this study. In the present study, the patients were, on average, three years younger, and sleep complaints were observed in 62% of the patients, which was lower than in Blattner's study.

Erkent (2023) [27] examined 17 patients with autoimmune encephalitis in Turkey. The average age of the patients was 50 years, and 9 were male. The final diagnoses of sleep disorders included circadian rhythm sleep disorder, periodic limb movement syndrome, insomnia, central apnea with or without respiratory effort, obstructive sleep apnea, and NREM parasomnia. In the current study, the average age of the patients was 50 years.

In a study conducted by Yan in China in 2021 [28], 119 patients with NMDAR autoimmune encephalitis underwent examination. Autonomic dysfunction was observed in 61.3% of patients, with tachycardia being the most prevalent symptom in 69.6% of cases. In the current study, autonomic dysfunction was also noted in approximately 62.9% of cases, which aligns with Yan's study, although hypertension exhibited the highest prevalence in our study.

In a qualitative study, Koo (2023) [29] emphasizes that sleep disorders are a common and critical aspect of autoimmune encephalitis. Hypersomnia, narcolepsy, insomnia, OSA (obstructive sleep apnea), parasomnias, and PLMS (periodic limb movement syndrome) are often associated with autoimmune encephalitis. Identifying sleep problems can help mitigate their consequences. In the current study, the most sleep disorders were related to insomnia, followed by hypersomnia and sleep apnea, which is different from the results of Koo's study, as in his study, hypersomnia was the most common, but in the current study, hyposomnia was the most common.

In another descriptive study, Ralls (2022) [30] mentions that sleep/wake disturbances are common in patients with autoimmune encephalitis, sometimes the most prominent or sole initial symptom, leading to delayed diagnosis. Autoimmune encephalitis mediated by N-methyl-D-aspartate receptor (NMDAR) antibodies is often associated with insomnia, followed by hypersomnia and Sleep Apnea. Severe sleeplessness and RBD are seen in patients with complex potassium channel antibodies. Fragmented sleep and hypersomnia are common in paraneoplastic syndromes associated with anti-Ma antibodies. RBD has

been observed in individuals with antibodies against leucine-rich glioma-inactivated protein (LGI1) or contactin-associated protein 2 (CASPR2). Antibodies against IGLON5 may lead to obstructive sleep apnea, stridor, NREM, and excessive movements. This study was similar to the current study in terms of prevalence of insomnia, hypersomnia and sleep apnea in patients with NMDAR antibody type.

In the study by Ariño (2020) [31], sleep disturbances were reported to be common among patients with anti-NMDAR encephalitis, which is consistent with the findings of the present study.

Differences in the reported prevalence of sleep and autonomic disturbances across studies are likely due to methodological heterogeneity. First, the composition of autoimmune encephalitis subgroups in each study may influence the pattern of clinical manifestations. In the present study, the higher prevalence of concurrent sleep and autonomic disturbances among patients with seronegative and anti-NMDA antibodies may reflect a phenotype pattern dependent on antibody type. Second, the timing of patient assessment relative to the disease phase (acute, subacute, or chronic) can affect symptom severity, with evaluations conducted during the acute phase being more likely to detect more pronounced disturbances. Furthermore, the lack of a significant association between abnormal EEG and MRI findings and autonomic dysfunction in our study may suggest that these disturbances are primarily driven by functional network dysregulation rather than by structurally detectable lesions on conventional imaging.

One of the limitations of this study is the small sample size of autoimmune encephalitis patients. It is recommended that multicenter studies be conducted.

5. Conclusion

The findings indicate that the prevalence of sleep and autonomic disturbances in the autoimmune encephalitis patients is higher than that observed in the general population and is not necessarily associated with structurally detectable lesions on conventional imaging. Antibody type may also serve as a potential indicator of increased risk for these disturbances.

Moreover, hypertension, as one of the most common manifestations of autonomic dysfunction, can significantly affect multiple aspects of a patient's daily life and overall medical condition. Therefore, routine screening for sleep disturbances and autonomic dysfunction in these patients is strongly recommended, along with the implementation of appropriate preventive and therapeutic interventions.

CRediT authorship contribution statement

Masoud Etemadifar: Writing – review & editing, Project administration. **Abbas Beiranvand:** Validation, Investigation, Formal analysis. **Sajad Parvar:** Resources, Investigation, Data curation. **Mohammad Jamshidpour:** Visualization, Funding acquisition, Formal analysis. **Donya Sheibani Tehrani:** Writing – original draft, Software, Methodology.

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Research Ethics Committees of School of Medicine - Isfahan University of Medical Sciences (IR.MUI.MED.REC.1401.009).

Ethics approval and consent to participate

The current study was approved by the Isfahan University of Medical Sciences Ethics Committee with the code of IR.MUI.MED.REC.1401.009.

Ethical issues

Written consent was obtained from the families of patients to enter this study.

Consent for publication

All coauthors have seen and agree with the contents of the manuscript and each author believes that the manuscript represents honest work. All coauthors certify that the submission is not under review at any other publication. There are no previous reports that might be regarded as redundant publication of the same or very similar work. Furthermore, the authors report no conflict of interest.

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Availability of data and materials

The data that support the findings of this study are available but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [**Donya Sheibani Tehrani**].

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

The study data are available from the corresponding author upon request.

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