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SHORT COMMUNICATION

Hypersomnia in anti-glutamic acid decarboxylase 65 (GAD65) associated neurological syndromes: A pilot study

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Abstract

Background and purpose: Despite their detrimental impact on the quality of life in autoimmune encephalitis, sleep disorders have not been investigated in anti-glutamic acid decarboxylase (GAD65) associated neurological syndromes.

Methods: Six consecutive adult patients diagnosed with anti-GAD65-associated neurological syndromes (four with limbic encephalitis and two with stiff-person syndrome) and 12 healthy controls were enrolled. Participants underwent sleep interviews and sleep studies including night-time video-polysomnography, followed by five daytime multiple sleep latency tests (MSLTs, to assess propensity to fall asleep) and an 18 h bed rest polysomnography (to assess excessive sleep need).

Results: Patients reported the need for daily naps and that their cognition and quality of life were altered by sleepiness, but they had normal scores on the Epworth sleepiness scale. Compared with controls, sleep latencies during the MSLT were shorter in the patient group (median 5.8 min, interquartile range [IQR] 4.5, 6.0 vs. 17.7 min, IQR 16.3, 19.7, $p = 0.001$), and the arousal index was reduced (2.5/h, IQR 2.3, 3.0 vs. 22.3/h, IQR 13.8, 30.0, $p = 0.002$), although total sleep time was similar between groups (621 min, IQR 464, 651 vs. 542.5 min, IQR 499, 582, $p = 0.51$). Remarkably, all six patients had MSLT latencies ≤8 min, indicating severe sleepiness. No parasomnia or sleep-disordered breathing was detected.

Conclusion: Central hypersomnia is a relevant characteristic of anti-GAD65-associated neurological syndromes.

KEYWORDS
autoimmune diseases of the nervous system, encephalitis, epilepsy, hypersomnia, hypersomnolence, stiff-person syndrome

Lina Jeantin, Ana Gales, Dimitri Psimaras and Isabelle Arnulf contributed equally to this work.

INTRODUCTION

Autoimmune encephalitis (AE) is characterized by neuropsychiatric symptoms, including cognitive impairment, epilepsy and sleep disturbances [1]. Despite their impact on the quality of life of AE survivors, sleep problems remain frequently underreported by patients and overlooked by clinicians. However, specific sleep disorders are prevalent amongst AE patients (reviewed in references 2–4), including rapid eye movement (REM) sleep behaviour disorder (RBD) and narcolepsy in anti-Ma2 encephalitis, insomnia during the acute phase of *N*-methyl-D-aspartate receptor encephalitis (followed by hypersomnia in the post-acute phase), non-REM/REM parasomnias and hypoventilation in anti-IgLON5 encephalitis, insomnia and parasomnias in anti-contactin-associated protein-like 2 (CASPR2) encephalitis, as well as insomnia in anti-leucine-rich glioma-inactivated 1 (anti-LGI1) encephalitis [2–4].

In contrast, sleep disorders have not been studied in anti-glutamic acid decarboxylase 65 (GAD65) associated neurological syndromes (NS) [2–4]. Anti-GAD65-associated NS can present most commonly as limbic encephalitis (including temporal seizures and cognitive impairment) or stiff-person syndrome (SPS, including muscle stiffness), but also as isolated neuropsychiatric symptoms (apathy, behaviour changes, anxiety), cerebellar ataxia or progressive encephalomyelitis with myoclonus [5]. Sleep and wake were investigated in six patients with anti-GAD65-associated NS.

METHODS

Participants

Patients diagnosed with anti-GAD65-associated NS at Pitié-Salpêtrière University Hospital between August 2019 and December 2022 were prospectively enrolled. Inclusion criteria were as follows: (i) clinical manifestations consistent with anti-GAD65-associated NS [5]; (ii) identification of anti-GAD65 antibodies in serum or cerebrospinal fluid through indirect immunohistochemistry, subsequently confirmed by immunoblot analysis; (iii) ability to provide informed consent. Each patient was paired with two healthy controls of matching gender and age, who had been recruited by advertisement from the general population in a previous study [6]. They had no medical, mental or sleep disorders and no drug intake [6].

Sleep studies

Patients and controls underwent face-to-face interviews with a sleep specialist, completed the Epworth Sleepiness Scale (ESS) at the time of video-polysomnography (V-PSG) and the Functional Outcome of Sleep Questionnaire (FOSQ-10) as a follow-up questionnaire in January 2023. Additionally, participants were tested for the presence of HLA DQB1*0602 genotype. The sleep studies included V-PSG during night 1 from 9:00 PM to 6:30 AM, five multiple sleep latency tests (MSLTs) during day 2 and 18 h sleep recording from 9:00 PM to 3:00 PM on night 2 and day 3 [6]. The V-PSG included eight electroencephalography channels (F3/C3, C3/O1, C3/T3, T3/O1, F4/C4, C4/O2, C4/T4, T4/O2), two electrooculograms, chin and tibialis anterior muscle electromyography, nasal pressure and naso-oral thermistor, thoracic and abdominal plethysmography, transcutaneous oxyhaemoglobin, pre-tracheal microphone, electrocardiogram and synchronous infrared video and audio recordings. Sleep stages and events (including periodic leg movements and tonic REM sleep without atonia defined as enhanced tonic chin muscle tone for more than 50% of REM sleep epochs) were visually scored by two neurologists according to the *American Academy of Sleep Medicine* manual, version 2.6 [7]. Hypersomnia was defined as a mean sleep latency of <8 min during MSLTs [8].

Ethics and consent

Informed written consent was obtained from patients and controls. In patients, the use of routine sleep measures for research purposes was authorized through the non-opposition procedure, which waived the requirement for ethics committee approval under French law. Healthy controls participated in a previous study approved by the ethical committee [6] and received compensation for their participation. The study was performed in accordance with the ethical standards from the 1964 Declaration of Helsinki and its amendments.

Statistical analysis

Results are described as count and frequency for categorical variables and median and interquartile range (IQR) for quantitative variables. Statistical analyses were performed using R statistical software version 3.5.2. Fisher's exact test was used to compare categorical variables and the Wilcoxon rank-sum test to compare quantitative variables.

RESULTS

Patient characteristics

Six consecutive patients with anti-GAD65-associated NS were enrolled. Their clinical, imaging and biological data are presented in Table S1. Five patients were women, with a median age at diagnosis of 32.5 (IQR 29.2, 53) years. Four had limbic encephalitis and two had SPS. Two patients were recorded in the chronic phase with clinical stability, three in the subacute phase with continuous clinical improvement and one in the subacute phase with worsening SPS (Figure 1). At the time of sleep studies, the median disease

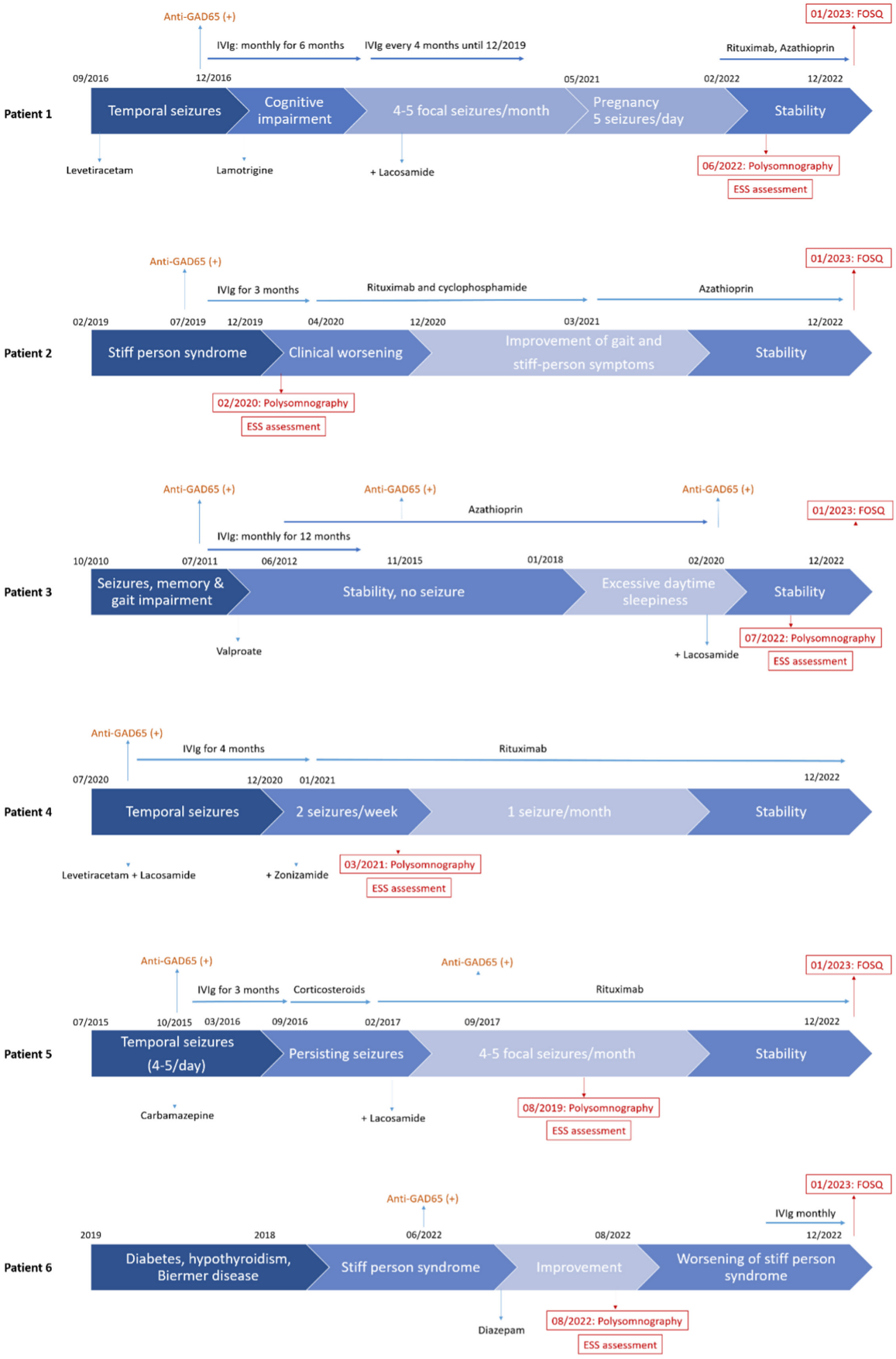

FIGURE 1 Timing of sleep studies relative to initial diagnosis in six patients with anti-GAD65-associated neurological syndromes. +, positive; ESS, Epworth Sleepiness Scale; GAD65, glutamic acid decarboxylase 65; IVIg, intravenous immunoglobulins.

duration was 57 (IQR 22, 67) months. All but one patient received immunomodulatory treatment (Figure 1). Other medications included benzodiazepines ($n=5$), levetiracetam ($n=3$) and lacosamide ($n=3$).

Sleep interview

A higher number of patients than controls experienced sleep attacks (3 vs. 0) and an excessive need for sleep (5 vs. 0; see Table 1). However, the median ESS score was comparable between the two groups. In the FOSQ questionnaire administered to five of six patients, all participants indicated daily naps, as well as memory and attention problems linked to sleepiness.

Sleep study

On the sleep electroencephalography, three (50%) patients had temporal slow waves (no spike or spike and wave) and none had any night-time seizure. Three (50%) patients had tonic REM sleep without atonia (RWA) for greater than 18% of REM sleep time, but none displayed REM sleep behaviour disorder, either on the concomitant video or at home [8]. No patient had non-REM parasomnias (including behaviours in stage N2 and arousal disorders in stage N3). No stridor, catathrenia, sleep apnoea syndrome and sleep-associated hypoxaemia were observed. During the first night (terminated at 6:30 AM), sleep onset and REM latencies, total sleep time and sleep stage distribution did not differ between patients and controls (Table 1). The arousal index and periodic leg index were lower in patients than in controls. Total sleep time during the 18 h bed rest period did not differ between groups (Figure S1). The mean MSLT latency was shorter in patients than in controls (Table 1). MSLT latencies were below 8 min in all patients. During MSLTs, three patients and no controls had a single sleep onset in REM (SOREM) period, and none had two or more SOREM periods.

DISCUSSION

In this systematic pilot study, six patients with anti-GAD65-associated NS exhibited hypersomnia characterized by short daytime sleep latencies during MSLTs, independently of disease phase (subacute or recovery), phenotype (limbic encephalitis and SPS) and medication. Additionally, the patients had a more continuous night-time sleep than healthy controls.

To our knowledge, this is the first study reporting interviews and sleep studies in patients with anti-GAD65-associated NS. Although MSLT latencies were abnormally short, there were no SOREMs or cataplexy, as observed in narcolepsy type 1 [9]. This hypersomnolence was associated with normal (five patients) or long (one patient) total sleep time, and uninterrupted, continuous sleep (including low arousal index, absence of sleep apnoea, seizures, movement disorders and parasomnia). These characteristics suggest a central hypersomnia linked to the autoimmune disease [8]. Whilst most patients reported a daily need for naps and sleepiness-induced cognitive, memory and quality-of-life impairments, the ESS scores were normal, suggesting impaired sleepiness perception.

The absence of stridor and catathrenia, along with a normal apnoea–hypopnoea index, implies that anti-GAD65 antibodies do not impede brainstem control of upper airway patency, differing from anti-IgLON5-associated encephalitis [4]. The macro- and micro-architecture of sleep in patients with anti-GAD65-associated NS was remarkably normal. Half of patients exhibited REM sleep without atonia, but no RBD or non-REM parasomnia, unlike anti-LGI1 and anti-IgLON5 encephalitis [4]. Collectively, these findings suggest that anti-GAD65 antibodies exert minimal influence on sleep generators, but could impact arousal systems. These systems, located in the brainstem and hypothalamus, house histamine, norepinephrine, dopamine, serotonin and hypocretin-1 neurons [10]. Some of these neurons (although probably not hypocretin-1 neurons in the absence of cataplexy and SOREMs) may be targeted by anti-GAD65 antibodies. Additionally, the potential influence of medication cannot be excluded, as benzodiazepines and antiepileptic drugs (which could not be safely withdrawn) can be sedative [11]. The MSLT latencies, however, are particularly short for resulting only from a drug effect, suggesting a predominant encephalitis-related role in this hypersomnia.

Excessive daytime sleepiness has been reported in other forms of AE. Hypersomnia was documented during the recovery phase of anti-*N*-methyl-D-aspartate receptor associated encephalitis [12], although MSLTs were not conducted. Narcolepsy is prevalent in patients with anti-Ma2-associated encephalitis [13–15]. A patient with anti-Ma2-associated encephalitis was treated with pitolisant, a wake-promoting drug that increases brain histamine release [15]. Pitolisant is an interesting option for alleviating hypersomnolence in patients with epilepsy (common in AE) because it does not lower the epileptic threshold (unlike methylphenidate) or interfere with other drugs (unlike modafinil). It could be an option for people with hypersomnolence and anti-GAD65-associated NS, after MSLT has demonstrated objective sleepiness (if required by local regulations). As night-time sleep was remarkably normal, extended night-time sleep studies may not be mandatory in routine care.

Our study has several limitations, including a reduced sample, two different GAD65-associated NS phenotypes, varying intervals from the onset of symptoms and use of medications. The nature of a field study, the impossibility to safely withdraw medications, and the rarity of anti-GAD65-associated NS make it challenging to obtain larger samples without confounding factors.

In sum, these six patients with GAD65-associated NS (although assessed at different disease stages, clinical presentations and after different types of treatment) all presented with hypersomnia characterized by shortened sleep latencies during MSLTs, which could be a novel and prevalent feature of anti-GAD65-associated syndromes. Evaluating sleep could clarify complex diagnoses and improve patient management and quality of life.

TABLE 1 Sleep symptoms and measures in patients with anti-GAD65-associated neurological syndromes and healthy controls matched for age and sex.

	Patients ($n=6$)	Controls ($n=12$)	p value
Demographic characteristics			
Female gender	5 (83.3)	10 (83.3)	1.00
Body mass index (kg/m^2)[b]	21.9 (19.6, 22.0)	23.9 (22.4, 26.7)	0.09
Age at the time of the sleep study (years)	38.5 (30.2, 55.8)	37.5 (31.5, 48.0)	0.78
HLA DQB1 0602 genotype	1 (16.7)	2 (16.7)	1.00
Sleep interview			
Cataplexy	0 (0)	0 (0)	—
Sleep-related hallucinations	0 (0)	0 (0)	—
Sleep respiratory symptoms (snoring, apnoea…)	0 (0)	0 (0)	—
Frequent nightmares	1 (16.7)	0 (0)	0.33
Restless leg syndrome	0 (0)	0 (0)	—
Excessive need for sleep	5 (83)	0 (0)	**0.002**
Sleep attacks	3 (50)	0 (0)	**0.004**
Epworth Sleepiness Score (/24)	6.5 (4.0, 9.8)	6.0 (5.8, 9.0)	0.89
FOSQ-10 score	15 (13, 17)	Not done	—
EEG characteristics on polysomnography			
Alpha background frequency (Hz) during wake[c]	10 (8.5, 10)	10 (9, 10)	0.77
Seizures during recordings[a]	1 (16.7)	0 (0.0)	0.33
Sleep measures during night 1 (adaptation night, stopped at 6:30 AM)			
Sleep latency (min)	12 (7, 15)	29 (24, 31)	0.09
REM sleep latency (min)	125 (104, 310)	122 (80, 174)	0.51
Total sleep time (min)	385 (325, 400)	407 (341, 446)	0.45
Sleep stages (%)			
N1	2.5 (1.4, 4.9)	5.0 (2.4, 6.5)	0.51
N2	55.7 (52.0, 56.4)	53.3 (47.9, 56.8)	0.45
N3	19.9 (18.3, 26.1)	23.8 (21.5, 27.9)	0.19
REM	17.1 (13.3, 23.6)	15.6 (12.6, 19.8)	0.789
REM without atonia >18%, *N* (%)	3 (50)	0 (0)	**0.004**
Sleep fragmentation, events/h of sleep			
Arousals	2.5 (2.3, 3.0)	22.3 (13.8, 30.0)	**0.002**
Periodic leg movements	0.0 (0.0, 0.0)	0.9 (0.3, 1.8)	**0.001**
Apnoea–hypopnoea	0.0 (0.0, 1.0)	1.2 (0.2, 2.9)	0.10
3% oxyhaemoglobin desaturation	0 (0, 0.8)	—	
Time spent with SaO2 < 90% (min)	0 (0, 0)	—	
Multiple sleep latency tests (day 2)			
Mean sleep latency (min)	5.8 (4.5, 6.0)	17.7 (16.3, 19.7)	**0.001**
Sleep onset in REM (SOREM) period, *N*	0.5 (0.0, 1.0)	0 (0.0, 0.0)	**0.01**
Mean sleep latency ≤8 min	6 (100)	0 (0)	**0.0002**
Mean sleep latency ≤8 min plus ≥2 SOREM periods	0 (0)	0 (0)	—
Sleep measures during night 2 (unrestricted night)			
Total sleep time (min)	487 (404, 525)	518 (492, 559)	0.35
Number with night-time sleep time > 10 h	1 (16.7)	2 (16.7)	1.00
Sleep measures during day 3 (bed rest, nap time from morning awakening to 03:00 PM)			
Total sleep time (min)	94.5 (63, 106)	16.5 (3.8, 30.5)	**0.003**
Sleep measures during 18 h bed rest (night 2 plus day 3)			
Total sleep time (min)	621 (464, 651)	542.5 (499, 582)	0.51
Number with total sleep time > 11 h/18 h	1 (16.7)	1 (8.3)	1.00

Note: Results are expressed as number (%) or median (interquartile range).

Abbreviations: EEG, electroencephalography; FOSQ-10, Functional Outcome of Sleep Questionnaire 10; GAD65, glutamic acid decarboxylase 65; MSLT, multiple sleep latency test; REM, rapid eye movement; SOREM, sleep onset in REM.

[a]Two brief partial temporal seizures during the MSLT.

[b]Data missing for one patient in the anti-GAD65 group.

[c]Data missing for one patient in the control group.

AUTHOR CONTRIBUTIONS

Lina Jeantin: Conceptualization; investigation; writing – original draft; methodology; visualization; writing – review and editing; software. **Ana Gales:** Conceptualization; writing – review and editing; visualization. **Giulia Berzero:** Writing – review and editing. **Smaranda Leu:** Writing – review and editing. **Jérémy Proust:** Writing – review and editing. **Marine Giry:** Writing – review and editing. **Nefeli Eirini Valyraki:** Writing – review and editing. **Cristina Birzu:** Writing – review and editing. **Agusti Alentorn:** Writing – review and editing. **Marie Vidailhet:** Writing – review and editing. **Dimitri Psimaras:** Writing – review and editing. **Isabelle Arnulf:** Supervision; writing – review and editing; methodology; validation.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS AND CONSENT

Informed written consent for the use of video-polysomnography data was obtained from patients.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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