# The Expanding Field of Autoimmune Sleep–Wake Disorders—Implications for the Movement Disorders Clinical Practice

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Movement Disorders
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IN FOCUS

# The Expanding Field of Autoimmune Sleep–Wake Disorders—Implications for the Movement Disorders Clinical Practice

**Devine MF, Feemster JC, Lieske EA, et al. Objective sleep profile in LGI1/CASPR2 autoimmunity. *Sleep* 2022; 45(2): zsab297.**

Rapid eye movement (REM) sleep behavior disorder (RBD), a parasomnia, has long been considered to be a herald of neurodegenerative disease, in particular α-synucleinopathies. Sleep–wake disorders are now increasingly recognized in autoimmune neurological disease and may even lead to the discovery of new entities, like in the case of anti-IgLON5 disease.[1,2] This increasing interest in autoimmune-mediated sleep–wake disorders led Devine and colleagues[3] to retrospectively assess clinical and polysomnography (PSG) features in a cohort of nine patients with leucine-rich, glioma inactivated 1 (LGI1) and two with contactin-associated protein-like 2 (Caspr2) antibodies.

The overall spectrum of clinical sleep-related disturbances in this cohort encompassed insomnia, dream enactment behavior (DEB) (both together in 63.6% of cases), excessive daytime sleepiness (hypersomnia, 36.4%) and snoring (72.7%). DEB was only observed in the LGI1 subgroup (56%).

On PSG, 73% of patients were diagnosed with obstructive sleep apnea, and when compared to age and sex-matched controls, patients with LGI1/CASPR2 antibodies showed altered sleep architecture with increased N1 and decreased REM sleep. Increased rates of REM sleep without atonia (RSWA), a correlate of RBD, were only found in patients with LGI1 antibodies. In fact, 88.9% of LGI1+ subjects fulfilled the RSWA diagnostic thresholds for RBD—when calculated according to RSWA diagnostic standards established previously from the same research group[4]—although only one without DEB fulfilled the American Academy of Sleep medicine (AASM) criteria for RSWA in RBD.

Therefore, RSWA may have been overlooked with the sole use of AASM criteria. The notion that RSWA seems to be a key quantitative polysomnographic feature also in patients with LGI1 antibodies, is one of the main and most interesting findings of this first attempt to systematically and quantitatively assess RSWA in autoimmune neurological disease. However, sleep disorders and PSG findings should only be looked in the context of the whole clinical phenotype.

In addition, in LGI1+/CASPR2+ patients sleep–wake symptoms preceded the neurological manifestations in 27.3%, developed in parallel in 45.5%, and occurred after the neurological manifestations in 18.1%. This might offer a window of opportunity for earlier recognition and treatment. Immunotherapy in this cohort was installed only after full clinical manifestation, but led to an overall neurological improvement and in 50% to an additional improvement of sleep–wake symptoms.

More research in this emerging area is needed. For example, actigraphy recordings rather than PSG could provide better real-life data, which may prove a useful marker for insomnia detection and monitoring. Given the frequent occurrence of cognitive impairments in these patients, objective measurements like the multiple sleep latency tests might be preferable to the Epworth sleepiness scale.

From a pathophysiological point of view, future studies of autoimmune-mediated sleep–wake disorders, in which targets of autoimmunity are known in detail, may facilitate a better understanding of the pathophysiology of specific sleep–wake disorders. For clinical practice, it is important to be aware that RSWA and sleep–wake disorders are not only heralding synuclein-related neurodegeneration, but also autoimmune disease (Table 1).

## Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Design, B. Execution, C. Review and critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

E.E.: 1A, 1 C, 3A
C.B.: 3B
B. B.: 1A, 3B

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**TABLE 1** *Summary of sleep symptoms and V-PSG findings in autoimmune encephalitis and neurodegenerative disease*

| Summary | Autoimmune encephalitis[2] | Neurodegenerative disease[5] |
|---|---|---|
| Sleep symptoms | | |
| Insomnia | NMDAR (GluN1), AMPAR (GluA1, GluA2)[a], LGI1, Caspr2, IgLON5, DPPX, mGluR5[b] | PD, DLB, MSA, PSP, AD, HD |
| Hypersomnia (EDS) | NMDAR (GluN1), AMPAR (GluA1, GluA2)[a], LGI1[a], IgLON5, DPPX[a], mGluR5[b] | PD, DLB, MSA, HD, ALS |
| V-PSG findings | | |
| RBD | LGI1, IgLON5, DPPX[a] | PD (50%), DLB (80%), MSA (80%–100%), SCA3 (50%); (PSP, AD: very rare) |
| NREM parasomnia | NMDAR (GluN1)[c], IgLON5 | DLB[c], AD[c] |
| Quasi-purposeful behaviors | Caspr2, IgLON5, DPPX[a] | None |
| Narcolepsy | Ma2, AQP4 | None |
| Stridor | IgLON5 | MSA, SCA1 + 3[a], ALS |
| OSAS | IgLON5, DPPX[a] | MSA, AD, ALS |
| PMLS | Caspr2, IgLON5, DPPX | PD, SCA 1–3 and 6 |
| Ambiguous sleep | DPPX[a] | DLB |

*Note*: Ambiguous sleep = sleep stages cannot be differentiated.
Abbreviations: V-PSG, video-polysomnography; PD, Parkinson's disease; DLB, dementia with Lewy bodies; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; AD, Alzheimer's disease; HD, Huntington's disease; EDS, excessive daytime sleepiness; ALS, amyotrophic lateral sclerosis; RBD, REM sleep behavior disorder; REM, rapid eye movement; SCA, spinocerebellar ataxia; NREM, non-REM sleep; OSAS, obstructive sleep apnea; PMLS, periodic limb movements during sleep.
[a]Described in single case reports or in small case series,[2]
[b]Described in small case series.[6]
[c]Confusional arousals.

# Disclosures

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