

Grey zone between narcolepsy type 1 and type 2

Zona cinzenta entre narcolepsia tipo 1 e tipo 2

Dear Editor,

The third International Classification of Sleep Disorders (ICSD-3) defines narcolepsy as patients with periods of sleep attacks or excessive daytime sleepiness. Neurophysiology tests with unremarkable polysomnography and positive Multiple Sleep Latency Test scores establish the diagnosis of narcolepsy¹.

The difficulties in the differential diagnosis include secondary causes of excessive daytime sleepiness, narcolepsy, and other primary central hypersomnia disorders¹. Usually, narcolepsy type 1 is differentiated by the presence of immunological pathophysiology and the consequent lower levels of hypocretin-1².

Usually, narcolepsy type 1 patients have cataplexy and a CSF hypocretin-1 concentration ≤ 110 pg/mL or $< 1/3$ of mean values obtained in normal volunteers.² Interestingly, the ICSD-3 defines patients with excessive daytime sleepiness and lower CSF hypocretin-1 levels as having type 1 narcolepsy, even without cataplexy. In fact, measuring CSF levels of hypocretin-1 has been considered the best option for the diagnosis of type 1 narcolepsy¹.

However, the normal levels of hypocretin-1 are higher than 200 pg/mL². Indeed, there is a grey zone between 110 pg/mL and 200 pg/mL that is not discussed in the literature.

We describe three patients with hypocretin-1 levels between 110 pg/mL and 200 pg/mL (Table). All had the presence of allele HLA-DQB1*0602, sleep hallucinations, and sleep

paralysis. Two patients had all the criteria for narcolepsy type 1, but one of them did not have all the criteria for narcolepsy.

The hypocretin-1 threshold of 110 pg/mL has been identified by two studies². Quality Receiver Operating Characteristic curve analysis indicates a threshold of 200 pg/mL and 150 mg/mL for direct and extracted assays in volunteers, respectively^{3,4}. Although the biomarkers for identification of type 1 narcolepsy are very useful, the identification of patients with narcolepsy type 2 is still a challenge in many cases.

A paper written by Barateau et al. entitled *Comorbidity between central disorders of hypersomnolence and immune-based disorders*, expands this discussion.⁵ They state that the prevalence of immune diseases, inflammatory disorders, and allergies are not higher in narcolepsy type 1. Interestingly, autoimmune diseases were higher in narcolepsy type 2 patients and inflammatory disorders were common in idiopathic hypersomnolence.

Clinical and neurophysiology characteristics, genetics and hypocretin-1 levels are not sufficient to define narcolepsy in all circumstances. Unfortunately, the description of a few patients cannot characterize a pattern, especially in atypical cases. Further efforts to study patients with hypocretin-1 between 110 pg/mL and 200 pg/mL should help to classify them. It is possible that, in the future, biomarkers of inflammation and immune responses will be useful for that.

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Table. Demographic, clinical, genetic, and hypocretin-1 characteristics.

Age	HLA-DQB1*0602	CSF-HCRT (pg/mL)	MSLT/Average latency/(min)	MSLT/SOREMP	Cataplexy	Sleep paralysis	Hallucinations	Automatic behavior	Disruptive sleep
49	Yes	135.4	1	4	Yes	Yes	Yes	No	Yes
23	Yes	139.49	4	1	No	Yes	Yes	No	No
40	Yes	140.65	5	4	Yes	Yes	Yes	No	Yes

CSF: cerebrospinal fluid; HCRT: hypocretin; MSLT: Multiple Sleep Latency Test; SOREMP: sleep onset rapid eye moment period; min: minutes.

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References

1. Ruoff C, Rye D. The ICSD-3 and DSM-5 guidelines for diagnosing narcolepsy: clinical relevance and practicality. *Curr Med Res Opin*. 2016; 1-12.
2. Mignot E, Lammers GJ, Ripley B, Okun M, Nevsimalova S, Overeem S et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. *Arch Neurol*. 2002;59(10):1553-62. <https://doi.org/10.1001/archneur.59.10.1553>
3. Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Hypocretin (orexin) deficiency in human narcolepsy. *Lancet*. 2000;355(9197):39-40. [https://doi.org/10.1016/S0140-6736\(99\)05582-8](https://doi.org/10.1016/S0140-6736(99)05582-8)
4. Nishino S, Ripley B, Overeem S, Nevsimalova S, Lammers GJ, Vankova J et al. Low cerebrospinal fluid hypocretin (Orexin) and altered energy homeostasis in human narcolepsy *Ann Neurol*. 2001;50(3):381-8. <https://doi.org/10.1002/ana.1130>
5. Barateau L, Lopez R, Arnulf I, Lecendreux M, Franco P, Drouot X et al. Comorbidity between central disorders of hypersomnolence and immune-based disorders. *Neurology*. 2017;88(1):93-100. <https://doi.org/10.1212/WNL.0000000000003432>