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 narcolepsy.

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

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. 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 narcolepsy.

However, the normal levels of hypocretin-1 are higher than 200 pg/mL. 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 studies. 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. 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. 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.

<table>
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<tr>
<th>Age</th>
<th>HLA-DQB1*0602</th>
<th>CSF-HCRT (pg/mL)</th>
<th>MSLT/Average latency/(min)</th>
<th>MSLT/SOREMP</th>
<th>Cataplexy</th>
<th>Sleep paralysis</th>
<th>Hallucinations</th>
<th>Automatic behavior</th>
<th>Disruptive sleep</th>
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CSF: cerebrospinal fluid; HCRT: hypocretin; MSLT: Multiple Sleep Latency Test; SOREMP: sleep onset rapid eye moment period; min: minutes.
References


