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Autonomic dysfunction in idiopathic hypersomnia: an overlooked association and potential management

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There is a small yet robust body of literature regarding autonomic dysfunction in idiopathic hypersomnia as well as sleep disturbances in postural orthostatic tachycardia syndrome. This review aims at summarizing the current literature and highlighting gaps in the current knowledge. This article additionally presents the personal experience of one of the authors at the sleep center.

Keywords: idiopathic hypersomnia, autonomic dysfunction, postural orthostatic tachycardia syndrome, excessive daytime sleepiness

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CLINICAL SCENARIO

A 33-year-old woman with a decade-long history of excessive daytime sleepiness and no other known medical problems presented to our clinic for evaluation. She also experienced orthostasis when getting out of bed in the morning with associated nausea and abdominal pain.

She was diagnosed with idiopathic hypersomnia (IH) based on an overnight polysomnogram and a multiple sleep latency test performed in our sleep lab. The former showed a total sleep time of 767 minutes, while the multiple sleep latency test showed a mean sleep latency of 7 minutes with no sleep onset rapid eye movement (REM) periods. She was started on amphetamine and dextroamphetamine 20 mg a day with some symptomatic relief. She, however, was not able to maintain a regular 9–5 job because of the long sleep need and instead worked flexible hours from home. This flexibility of her work schedule allowed her to stay in bed up to 11 hours some days. On a subsequent clinic visit, interval events included a gastroenterology evaluation, where she was diagnosed with idiopathic gastroparesis confirmed by slowed gastric emptying. After this diagnosis we further investigated additional autonomic dysfunction in relation to her IH. The patient underwent autonomic testing. We performed a quantitative sudomotor axon reflex test, where electrophoresing acetylcholine is injected into the skin to stimulate muscarinic receptors on sweat glands.[1] Results of the quantitative sudomotor axon reflex test showed decreased sweat response throughout consistent with small fiber neuropathy. As part of a neuropathy workup, we also discovered autoantibodies against neuronal antigens. To further test for cardiovagal functioning, heart rate response to deep breathing was quantified. The patient showed decreased heart rate variability to deep breathing. Finally, a Valsalva maneuver and a head-up tilt test were performed to determine the integrity of the patient's adrenergic functioning and test for orthostatic hypotension. The Valsalva maneuver is forced exhalation against a closed airway. The response to this maneuver consists of five different phases: Phase I, during which the blood pressure (BP) rises upon blowing air, early phase II (II-E), which corresponds to a drop in BP due to the decreased preload to the heart, late phase II (II-L) during which BP rises due to the baroreceptor reflex, phase III where there is a transient decrease in BP, and phase IV corresponding to BP recovery.[1] The patient presented with an absent II-L. The head-up tilt test, which determines the heart rate and BP in response to a head tilt,[1] was aborted after 2 min, 40 seconds for presyncope. This was consistent with the diagnosis of autonomic dysfunction and the findings were like those seen in postural orthostatic tachycardia syndrome (POTS). At the neuromuscular clinic, to where she was referred after the abnormal quantitative sudomotor axon reflex test and serology, she was started on intravenous immunoglobulin (IVIG) treatment which improved all her symptoms albeit to various degrees. Her neurologist started the IVIG as a treatment for the autonomic dysfunction and not for her hypersomnia. The modest improvement in her daytime sleepiness was unexpected.

The mechanism of autonomic dysfunction in patients with IH and that of sleep disturbances in POTS are both poorly understood. However, it is important to recognize autonomic comorbidities with IH and daytime sleepiness in POTS.[2,3]

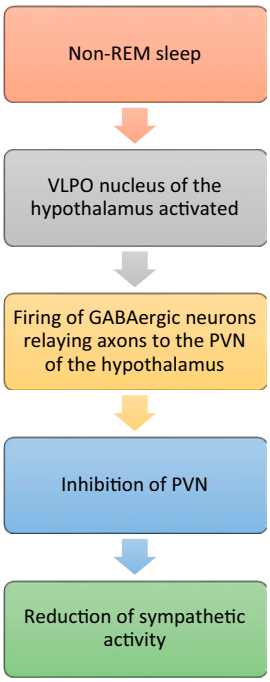
IH AND AUTONOMIC DYSFUNCTION

Symptoms of autonomic nervous system dysfunction are common in IH including resting tachycardia[4] and orthostatic intolerance.[5] In a cohort of 138 IH patients and 81 controls Miglis et al used online surveys for assessment excessive daytime sleepiness, insomnia quality of life (including physical, mental,

and general health), and autonomic symptoms through the Composite Autonomic Symptom Score-31 (COMPASS-31). The latter assesses autonomic functioning on six different domains which include secretomotor, vasomotor, pupillomotor, gastrointestinal, orthostatic intolerance, and urological. IH patients had a higher autonomic symptom burden in all six domains, and this was positively correlated with sleepiness and negatively correlated with quality of life.[6] The well-established involvement of the autonomic nervous system during sleep might help us further understand the autonomic dysregulation in IH. In non-REM sleep, the sympathetic nervous system activity is decreased, while the parasympathetic nervous system increases its functioning. This occurs through the ventrolateral preoptic nucleus of the hypothalamus that, through GABAergic connections to the paraventricular nucleus, leads to its inhibition. This, therefore, reduces the sympathetic activity. Furthermore, the nucleus of the solitary tract is responsible for regulation of BP and is a main contributor to the baroreceptor reflex. The pons (the part of the brain responsible for REM sleep) has glutamatergic connections with the nucleus of the solitary tract, suggesting one mechanism of BP regulation during sleep. In fact, going to sleep induces a 10–20% decrease in BP compared to baseline values during the day. This phenomenon is described as the "dipping phenomenon".[2] Hypothetically these interrelated neuroanatomical pathways could underlie the coexistence of excessive daytime sleepiness and autonomic dysfunction in IH.

Please refer to **Figure 1** for a visual summary of autonomic nervous system function in sleep.

Figure 1—Functioning of the ANS in sleep.



ANS = autonomic nervous system, PVN = paraventricular nucleus, REM = rapid eye movement, VLPO = ventrolateral preoptic nucleus.

Nevertheless, the mechanism of autonomic dysfunction in IH is still unknown but can be postulated to be due to reduced physical activity or immune dysregulation.[6,7] Parsaik et al in a cohort of 84 participants with autonomic dysfunction and 100 controls demonstrated that orthostatic intolerance was strongly and independently associated with lack of physical activity, and hence deconditioning.[8] Since then, this has been also demonstrated in both animal models[9] as well as other human studies,[10] albeit both studies were in the setting of chronic pain. Finally, in cohort of 83 pediatric patients with primary hypersomnias, 33 (37%) demonstrated orthostasis. Eleven of the 33 had IH while the rest had either narcolepsy, secondary hypersomnia, or periodic hypersomnia.[11]

IH AND IMMUNE DYSREGULATION

The support to the immune dysregulation theory comes from two distinct findings. The first is the discovery of higher prevalence of autoinflammatory conditions (sarcoidosis, psoriasis, myelitis, asthma, eczema, and allergic rhinitis) in IH patients[7]. The second is the finding that autonomic dysregulation may be immune-mediated in certain neuroimmunolgical conditions such as multiple sclerosis. In multiple sclerosis, in addition to significantly contributing to disability, autonomic dysfunction may increase inflammatory burden. It is hypothesized that this occurs due to a dysfunction of the parasympathetic anti-inflammatory pathway as well as sympathetic changes and associated inflammatory processes.[12] Finally, Tanaka and Honda reported immunoglobulin (Ig) G levels abnormalities specific to IH. These included elevated IgG3 and IgG4 levels, decreased IgG2 levels, and IgG1/IgG2 imbalance.[13]

IH OVERLAP WITH POTS

There is an intriguing overlap between IH-related autonomic disfunction and POTS as both conditions are associated with profound Ehlers-Danlos syndrome. POTS is a form of dysautonomia characterized by increased sympathetic nervous system activation and orthostatic intolerance. Individuals affected with POTS often complain of Ehlers-Danlos syndrome. Persistent Ehlers-Danlos syndrome was reported in 40% of POTS patients, Ehlers-Danlos syndrome at least once weekly by 22%, and at least once per month by 20%.[14] Patients also had increased heart rate in sleep (r = .291; P = .02), especially in non-REM (r = .275; P = .034), and while awake and at rest in the supine position (r = .518, P = .01).[14] Several of the POTS patients also had nocturnal tachycardia and increased autonomic arousals.[14]

In another study, 25 POTS patients and 31 control participants filled out Pittsburgh Sleep Quality Index and Epworth Sleepiness Scale questionnaires. Compared to controls, POTS patients scored significantly higher on the Pittsburgh Sleep Quality Index of 8 (4–13) vs 4 (3–5) (P = .01).[15] POTS patients scored higher on the Epworth Sleepiness Scale as well, although this did not reach significance. On polysomnography

testing POTS patients had a higher mean heart rate in both non-REM and REM sleep and significantly higher percentage of stage N2 sleep than controls (42.45 vs 36.70%; $P = .017$).[15]

A distinctive feature of POTS as compared to IH with autonomic dysfunction is that POTS patients have also poor sleep efficiency on polysomnography and some also complain of insomnia[14,15]

Going back to our case, our patient achieved significant control of her daytime sleepiness, and to some degree her morning inertia, with a combination of Adderall XR 30 mg a day and IVIG treatments. We could not find in the medical literature any reports of use of IVIG in the treatment of IH. In our case it was started for her small fiber neuropathy and the IVIG's benefits in partially improving sleepiness and fatigue were incidental. In fact, her long sleep need of over 11 hours per night remains a concern. Her gastroparesis and other autonomic symptoms, however, significantly improved with IVIG. Some small fiber neuropathies have been reported to have autoantibodies against neuronal antigens.[15] Hence, this case highlights the association between IH and autonomic symptoms like POTS and potential immunological dysfunction as a potential contributor to these autonomic symptoms. A recent case series of 6 POTS patients treated with IVIG reported both improvement in autonomic symptoms as well as fatigue.[16]

As we learn more about the pathophysiology of IH as well as that of POTS we will be able to come up with better theories for the mechanism of autonomic dysfunction in these patients. For now, it is important to recognize autonomic comorbidities with IH and sleep disturbances in POTS. More work also needs to be done to evaluate the role of IVIG in the treatment of daytime sleepiness in these patients.

ABBREVIATIONS

BP, blood pressure
IH, idiopathic hypersomnia
Ig, immunoglobulin
IVIG, intravenous immunoglobulin
POTS, postural orthostatic tachycardia syndrome
REM, rapid eye movement

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