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Editorial

Exploration of autonomic activity in narcolepsy: The riddle remains unsolved

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Narcolepsy type 1 (NT1) is caused by the near-complete, possibly autoimmune-mediated loss of the hypothalamic neurons that release the hypocretin/orexin (H/O) neuropeptides (Kornum et al., 2017). The H/O neurons project to the neurons involved in sympathetic and parasympathetic control at multiple levels of the central autonomic network, as well as to excitatory and inhibitory projections that target these neurons (Bastianini and Silvani, 2018). This raises the questions whether and to what extent the loss of H/O neurons impairs autonomic control in patients with NT1.

These questions have proved to be a riddle. Early clinical investigations suggested that NT1 entails "reduced vegetative reactivity in the cardiovascular system" "mediated by both the sympathetic and parasympathetic systems", concluding that "the functional disturbance found probably is of central origin" (Sachs and Kaijser, 1980). A few clinical autonomic results of this early study could not be replicated (Grimaldi et al., 2014). However, its conclusions were echoed by more recent findings that the increases in heart rate in response to arousals and leg movements during sleep and the decreases in arterial blood pressure (ABP) and heart rate during sleep compared to wakefulness are attenuated in mouse models and/or patients with NT1 (Berteotti and Silvani, 2018). On the other hand, the values of ABP, heart rate, and muscle sympathetic nerve activity measured with peroneal microneurography were found significantly decreased during relaxed daytime wakefulness in patients with NT1 (Donadio et al., 2014). The investigation of sympathetic activity to the heart has lagged behind. The cardiac sympathetic nerves cannot be explored with microneurography in patients. The mean value of heart rate reflects both sympathetic and parasympathetic activity, and indexes of sympathetic activity based on heart rate variability such as the LF/HF ratio have been highly questioned by recent research (De Zambotti et al., 2018).

In this issue of *Clinical Neurophysiology*, Barateau et al. (2019) contributed to shed light on sympathetic cardiac control in patients with NT1 by employing ^{123}I-MIBG myocardial scintigraphy, which is generally employed for the diagnostic evaluation of pheochromocytoma and some forms of heart failure, neurogenic orthostatic hypotension, and neurodegenerative diseases (Goldstein and Cheshire, 2018). The main finding of their study was negative: no significant differences were detected in cardiac autonomic activity between NT1 patients and control subjects in crude and adjusted comparisons. There are a few caveats, acknowledged by the authors, that are worth being taken into account when interpreting these results.

First, the control group of the study by Barateau et al. (2019) was not drawn from a healthy population, but rather consisted of subjects who underwent scintigraphy for another reason, mostly to exclude a pheochromocytoma. Thus, the results might also be compatible with a scenario in which the NT1 patients and control groups had similar, yet both lower than normal values of ^{123}I-MIBG uptake. However, this scenario is made unlikely because control subjects had no neurological or sleep disorders, no heart failure, no diabetes mellitus, and took no drugs that may affect myocardial scintigraphy.

Second, the study by Barateau et al. (2019) relied only on the delayed heart/mediastinum (H/M) ratio of ^{123}I-MIBG. The uptake, storage, and release mechanisms of ^{123}I-MIBG are similar to those of norepinephrine. The delayed H/M ratio is a composite measure depending on the early ^{123}I-MIBG uptake and the subsequent ^{123}I-MIBG washout by cardiac sympathetic terminals. The early ^{123}I-MIBG uptake mainly reflects the distribution of cardiac sympathetic nerves and the uptake functions at the nerve endings. The ^{123}I-MIBG washout mainly reflects the synaptic vesicle release resulting from sympathetic tone (Goldstein and Cheshire, 2018; Yamashina and Yamazaki, 2007). Low values of the delayed H/M ratio may thus result from disparate structural (cardiac sympathetic denervation) and functional (increased cardiac sympathetic tone) alterations, which cannot be easily teased out in the study by Barateau et al. (2019). In a previous study, however, the same research group reported that patients with NT1 and rapid-eye-movement sleep behavior disorder (RBD) had lower values of the early H/M ratio than patients with idiopathic RBD, whereas the ^{123}I-MIBG washout rate did not differ significantly (Barateau et al., 2018). This suggests that RBD associated with NT1 does not entail cardiac sympathetic denervation, at variance with idiopathic RBD, which is most often a harbinger of synucleinopathies (Goldstein and Cheshire, 2018; Miyamoto et al., 2008). It would seem plausible to extrapolate this conclusion to all cases of NT1, regardless of RBD. On the other hand, the findings of Barateau et al. (2019) do not rule out functional alterations in cardiac sym-

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pathetic control in patients with NT1 in conditions different from those during scintigraphic scans, such as during nighttime sleep.

Some patients with NT1 in the study by Barateau et al. (2019) showed values of the delayed H/M ratio comparable to the lowest values in the control group. This is not surprising if one assumes a similar distribution of the delayed H/M ratio in NT1 patients and controls. Interestingly, however, the NT1 patients with relatively low values of the delayed H/M ratio tended to assume psychostimulants as part of their therapy, and to be older and have more cardiovascular comorbidities and higher values of body-mass index, microarousal index, and submentalis muscle electromyographic activity during REM sleep than the other NT1 patients. While a negative correlation between H/M ratio and age is expected (Nakajima et al., 2018), and increased body mass index and microarousal index might be associated with cardiovascular comorbidities, the mechanisms behind the link with REM sleep atonia are less clear. One possibility is that individual patients with NT1, RBD, and low H/M ratio may be at risk of developing a synucleinopathy (Barateau et al., 2018). Regardless, these data remind us that a few patients with NT1 do have cardiovascular comorbidities and possible alterations in cardiac sympathetic activity. Barateau et al. (2019) successfully classified NT1 patients as having or not REM sleep atonia based on the values of their delayed H/M ratio with receiver operating characteristic (ROC) curves. In perspective, the reverse might also be feasible, namely to discriminate patients with NT1 and low delayed H/M values based on the extent of REM sleep atonia, which can be computed automatically based on polysomnography data (Ferri et al., 2010).

In conclusion, the study by Barateau et al. (2019) published in this issue of *Clinical Neurophysiology* does not solve the riddle of whether and to what extent the loss of H/O neurons impairs autonomic control in patients with NT1. Nonetheless, it does contribute to the solution for two main reasons. First, it included direct measurements that did not support gross alterations in cardiac sympathetic innervation and function in patients with NT1 as a group. Second, it highlighted that some patients with NT1, and in particular patients with psychostimulant use and/or cardiovascular comorbidities, may have cardiovascular autonomic alterations. These patients may be worth identifying and following up in light of the reports of cardiovascular consequences of psychostimulant therapy (Bosco et al., 2018) and increased mortality (Ohayon et al., 2014) associated with NT1.

Conflict of interest

The author has no potential conflicts of interest to be disclosed.

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