Sleep Medicine 77 (2021) 82–87

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Activating autoantibodies against G protein-coupled receptors in narcolepsy type 1

Maija Orjatsalo [a, b, *], Eemil Partinen [b, c], Gerd Wallukat [d], Anniina Alakuijala [a, b], Markku Partinen [b, c]

[a] Department of Clinical Neurophysiology, HUS Medical Imaging Center, Helsinki University Hospital, Finland
[b] Department of Neurological Sciences, University of Helsinki, Helsinki, Finland
[c] Vitalmed Research Center, Helsinki Sleep Clinic, Valimotie 21, 00380, Helsinki, Finland
[d] Berlin Cures GmbH, Berlin, Germany

ARTICLE INFO

Article history:
Received 29 April 2020
Received in revised form
26 November 2020
Accepted 29 November 2020
Available online 5 December 2020

Keywords:
Narcolepsy type 1
Hypocretin
Orexin
β2 adrenergic receptor autoantibodies
M2 muscarinic receptor autoantibodies
Nociception receptor autoantibodies

ABSTRACT

Study objectives: Narcolepsy type 1 is a rare hypersomnia of central origin, which is caused by loss of hypothalamic neurons that produce the neuropeptides hypocretin-1 and -2. Hypocretin-containing nerve terminals are found in areas known to play a central role in autonomic control and in pain signaling. Cholinergic M2 receptors are found in brain areas involved with the occurrence of hallucinations and cataplexy. In addition to classical symptoms of narcolepsy, the patients suffer frequently from autonomic dysfunction, chronic pain, and hypnagogic/hypnopompic hallucinations. We aimed to test whether narcolepsy type 1 patients have autoantibodies against autonomic β2 adrenergic receptor, M2 muscarinic receptors, or nociception receptors.

Methods: We tested the serum of ten narcolepsy type 1 patients (five female) for activating β2 adrenergic receptor autoantibodies, M2 muscarinic receptor autoantibodies, and nociception receptor autoantibodies.

Results: Ten of ten patients were positive for muscarinic M2 receptor autoantibodies ($P < 0.001$), 9/10 were positive for autoantibodies against nociception receptors ($P < 0.001$), and 5/10 were positive for β2 adrenergic receptor autoantibodies ($P < 0.001$).

Conclusions: Narcolepsy type 1 patients harbored activating autoantibodies against M2 muscarinic receptors, nociception receptors, and β2 adrenergic receptors. M2 receptor autoantibodies may be related to the occurrence of cataplexy and, moreover, hallucinations in narcolepsy since they are found in the same brain areas that are involved with these symptoms. The occurrence of nociception receptor autoantibodies strengthens the association between narcolepsy type 1 and pain. The connection between narcolepsy type 1, autonomic complaints, and the presumed cardiovascular morbidity might be associated with the occurrence of β2 adrenergic receptor autoantibodies. On the other hand, the presence of the autoantibodies may be secondary to the destruction of the hypocretin pathways.

1. Introduction

Narcolepsy is a rare hypersomnia of central origin [1,2]. Patients with narcolepsy suffer from severe daytime sleepiness, disrupted nighttime sleep, and sleep-related hallucinations [3]. There are two subtypes. Narcolepsy type 1 (NT1) is characterized by cataplexy, a sudden loss of muscle tone while awake, and is caused by the loss of hypothalamic neurons that produce the neuropeptides hypocretin-1 and -2 (also known as orexin-A and -B) [1]. Hypocretin promotes wakefulness and inhibits rapid eye movement (REM) sleep [3]. NT1 may be caused by an autoimmune process [1,2]. Narcolepsy type 2

The work was performed at Vitalmed Research Center, Helsinki Sleep Clinic and at Berlin Cures GmbH, Berlin.

All authors have seen and approved the manuscript. Maija Orjatsalo conducted the statistical analysis.

* Corresponding author. Department of Clinical Neurophysiology, HUS Medical Imaging Center, Helsinki University Central Hospital Jorvi, P.O. Box 800, FI-00029 HUS, Finland.
E-mail address: maija.orjatsalo@helsinki.fi (M. Orjatsalo).

https://doi.org/10.1016/j.sleep.2020.11.038
1389-9457/

(NT2) includes many of the same symptoms, excluding cataplexy, but its cause is unknown [1].

Hypocretin-containing nerve terminals are found in areas known to play a central role in autonomic and cardiovascular regulation in the central nervous system, and also in the adrenal gland [4]. Hypocretin neurons modulate both sympathetic and parasympathetic outflow but are more involved with sympathetic regulation [4]. Hypocretin increases sympathetic tone and motor activity [3], and, as a consequence, decreased sympathetic tone would be expected in NT1 in humans. Autonomic dysfunction in narcolepsy is widely recognized and studied, but conflicting data has been reported regarding whether sympathetic or parasympathetic tone predominates in humans [5].

In addition, hypocretin 1 neurons project to the posterior horns of the spinal cord, where they modulate pain sensations and sensitivity, and act in spinal nociceptive transmission in the dorsal root ganglia [6]. Thus, hypocretin is involved in nociceptive transmission through supraspinal and spinal mechanisms, and pain is, expectedly, a quite common symptom in NT1 [6,7].

Autoantibodies (AABs) are molecules reacting with antigens that are part of the organism in which the AAB is produced [8]. Classical harmful AABs are usually somatically mutated IgG AABs that attack and disable pathways related to cell clearance, antigen receptor signaling, or cell effector functions, ie cause tissue injury [8]. The effect of AABs can be systemic or specific to a target organ [8]. Of note, some classical AABs are occasionally detected also in healthy individuals [8]. In addition to these classical AABs, a new class of functional agonistic or antagonistic G protein-coupled receptor (GPCR) targeting AABs was later found [9], and the knowledge of these AABs is constantly increasing [10]. GPCRs are expressed in various cell types: immune cells, adaptive immune cells, and in specific tissues [9]. GPCRs activate different intracellular signaling pathways in response to exogenous and endogenous factors [9]. Functional GPCR-targeting AABs can activate or inhibit intracellular signaling pathways, ergo, function as agonistic or antagonistic AABs, respectively [9], in the same way that classical receptor agonists/antagonists do.

β2 adrenergic receptor (β2AR) is a GPCR that is principally expressed in airway smooth muscle cells causing bronchodilation [11], but also in vascular smooth muscle causing vasodilation, in the heart causing positive inotropic and chronotropic effects (ie changes in beating frequency), in uterus and bladder causing relaxation, and in liver and skeletal muscle causing glycogenolysis [12]. Physiological responses of β2ARs are mediated by epinephrine and norepinephrine [12]. Activating β2AR AABs, which are IgG class pathogenic drivers, have previously been linked to vascular dementia and Alzheimer's disease [13], and chronic fatigue syndrome [14]. In turn, inhibiting β2AR AABs have been linked to allergic asthma [15,16]. The functional effects of β2AR AABs are not yet clearly known and the clinical relevance of these AABs is not yet demonstrated [10].

M2 muscarinic acetylcholine receptor (M2R) is a GPCR and its stimulation generally leads to the inhibition of adenyl cyclase and the activation of potassium channels [12]. M2Rs are expressed in the brain [17], gastrointestinal tract, and bladder, and mainly mediate the parasympathetic control of the heart [12,18]. M2R AABs have been associated with tachyarrhythmias [19]. Principally, much of their role in the disease pathophysiology is likewise yet unknown.

Another GPCR, the nociception receptor has several functions, including the modulation of pain signaling [20]. It is activated by its endogenous peptide ligand, nociceptin [20]. The nociception receptors probably act to inhibit cellular excitability and have a role in the modulation of neuronal activity and transmitter release [20], and nociception receptor activation may reduce pain sensation [20]. In primate models, selective nociceptin agonists (eg RO64-6198) have produced excellent analgesic effect [21]. Nociception receptors are expressed in peripheral nerve and visceral tissues, dorsal root ganglia, and the central nervous system [20].

We aimed to measure activating AABs to β2ARs, M2Rs, and nociception receptors in NT1 patients. These autoantibodies have never been studied in NT1 patients. We assumed that patients with NT1 would be positive for AAB activity.

2. Methods

2.1. Participants

In this case series, activating AABs against β2AR, M2R and nociception receptors were tested in a group of NT1 patients ($n = 10$) of the Helsinki Sleep Clinic between 2016 and 2018. The obtained serum was tested for antibodies in the Berlin Cures GmbH laboratory in Berlin, Germany. All the patients fulfilled the diagnostic criteria of NT1 by the American Academy of Sleep Medicine (AASM) International Classification of Sleep Disorders Version 3 (ICSD 3) [22] and had cerebrospinal fluid (CSF) hypocretin values less than 110 pg/mL. Demographic information and data on hallucinations and pain symptoms were received during neurological visits.

2.2. Measurements

The functional β2AR, M2R, and the nociception receptor AABs were identified and quantified using a modified and standardized bioassay [23,24]. The method to study β2AR and M2R AABs is based on the chronotropic effects of patient's IgG containing GPCR AABs on the beating frequency of cultured spontaneously beating neonatal rat cardiomyocytes. With the use of specific blockers and competitors, the GPCR AABs are specified for their targeted receptors, in this case β2ARs and M2Rs. The method is well accepted and validated, and it is described in more detail previously [10,25]. In the presence of β2AR AAB activity, the beating frequency of neonatal rat cardiomyocytes increases, whereas M2R AABs exert a negative chronotropic response [26]. The IgG-containing GPCR AAB dilution, prepared from the patients' serum, was introduced to the neonatal rat cardiomyocytes and the change in the beating frequency was observed. The presence of β2AR AABs was confirmed with next incubating the neonatal rat cardiomyocytes with selective β2AR antagonist ICI 118.551 (0.1 μM), and the change in the beating frequency was observed. In the same way, the presence of M2R AABs was confirmed with next incubating the neonatal rat cardiomyocytes with atropine and recording the change in the beating frequency. Furthermore, the presence of AABs against nociception receptors was confirmed by incubating the neonatal rat cardiomyocytes with J113397, a highly selective antagonist for the nociception receptor and by recording the change in beating frequency. The activity of the nociception receptor AABs represents the difference between the total AAB activity and the activity in the presence of the nociception receptor antagonist J113397 (1 μM) in cells pretreated with atropine (1 μM) or ICI118.551 to block the muscarinic or β2-adrenergic response, respectively.

One unit (U) of GPCR AAB activity corresponds to a one beat/min frequency change. The lower limit of detection for positive and negative chronotropic activity was calculated as 4.0 U and −4.0 U, respectively. GPCR AAB positivity was defined as ± 3 SD derived from the reference values of 100 healthy controls [13]. The calculated cut-off value was 8 or -8 beats/min. The reference values we used for the tested AABs to β2ARs and M2Rs were previously gathered from a group of 100 healthy volunteers [13]. There, 2/100 were positive for β2AR AABs, and none were positive M2R or

nociception receptor AABs. These controls from the validation study were used to test for statistical significance in this study [13]. To further ascertain the results, we did two additional control analyses. Firstly, we tested cardiomyocytes that were treated similarly to the experimental samples but without the antibody preparation, and secondly samples from 10 healthy subjects from a different Scandinavian study that was performed at the nearly same time and with the partially same cell preparations. These control samples did not exhibit any autoantibody activity.

2.3. Standard protocol approvals and patient consents

The institutional review board of Vitalmed Helsinki Sleep Clinic approved of the study and written informed consent was obtained from all the participants.

2.4. Statistical analyses

Statistical analyses were performed using Stata 14.2 (StataCorp, Texas, USA). Group comparisons for the dichotomous variables were conducted with Fisher's two-sided exact test. A P value < 0.05 was used to denote significance.

2.5. Data availability

Anonymized data will be shared by request from any qualified investigator.

3. Results

Table 1 depicts the clinical characteristics of the patients with NT1. Five of the patients were woman and five men. The average time span from the onset of symptoms to the time of the study in the NT1 group was 7.2 years (standard deviation 0.42). The NT1 diagnoses were confirmed by CSF hypocretin-1 measurements in all the patients. All of them had unambiguous cataplexy, and hallucinations while falling asleep, ie hypnagogic hallucinations, or waking up, ie hypnopompic hallucinations.

Table 2 shows the number of patients positive for β2AR, M2R, and nociception receptor AABs. Most of the patients with NT1 were positive for nociception receptor AABs and all of them were positive for M2R AABs. Half of the patients had at least weak β2AR AAB activity. The associations were statistically significant.

Table 3 depicts the chronotropic change in the presence of activating AABs of the NT1 patients positive for the AABs.

There were no association with the occurrence of nociception AABs and experienced stomach pain or with other type of pain, eg limb pain or headache ($P > 0.05$).

4. Discussion

All the NT1 patients in our study were positive for AABs against muscarinic M2 receptors and the prevalence of activating AABs against nociception receptors was significantly elevated in our NT1 patients compared to controls. In addition, half of the patients had at least weak β2AR AAB activity. As far as we know, this is the first time these autoantibodies have been studied.

Table 1
Clinical characteristics of narcolepsy type 1 patients in the study (N = 10).

Age (years)	26.0 (5.50)
BMI (kg/m^2)	25.8 (5.01)
ESS score ≥11	8/10
CSF hypocretin <110 pg/mL	10/10

Values are means with standard deviation or numbers of subjects. NT1: narcolepsy type 1; BMI: body mass index; ESS: Epworth Sleepiness Scale; CSF: cerebrospinal fluid.

In general, NT1 patients suffer from autonomic complaints [2], and might have an increased risk of cardiovascular diseases [27]. In a few studies, awake resting sympathetic tone was elevated [28,29]. Yet, using different methods, patients with NT1 displayed decreased peripheral sympathetic activity, heart rate (HR), and blood pressure (BP) during wakefulness [30]. Furthermore, CSF hypocretin-1 deficiency was correlated with peripheral sympathetic tone and heart rate, indicating a direct effect of hypocretin on autonomic regulation, ie, the loss of hypocretin decreasing sympathetic activity [30]. On the other hand, hypocretin levels have not been correlated to nocturnal or diurnal blood pressure in NT1 [30,31]. What is more, inconsistent results have also been obtained regarding awake resting parasympathetic tone, as in certain studies it was elevated, and in other studies attenuated [28,32]. Nocturnal cardiac autonomic nervous system functioning, measured in heart rate variability, might be similar in NT1 patients compared to controls [28,33], while nocturnal heart rate was higher [33], blood pressure dipping less frequent [34,35], and blunted heart rate response to arousals was observed [33,36]. Further, a direct measure of the heart adrenergic nerve activity, ^{123}I-Meta-iodobenzylguanidine (^{123}I-MIBG) myocardial scintigraphy, revealed no sympathetic denervation in NT1 [37]. Cardiac sympathetic activity did not correlate with CSF hypocretin levels, either [37]. This body of research could indicate that there is no true autonomic neuropathy in NT1. Still, NT1 patients suffer from a wide range of autonomic symptoms [2], and these symptoms ask for an explanation.

β2ARs and M2Rs are widely expressed in the autonomic nervous system [11,12,17,18], and their dysfunction, caused by activating autoantibodies, could be expected to induce autonomic disturbances. The basis of the pathogenic mechanism of these AABs against GPCRs is hypothesized to be the stabilizing of the active conformation of the GPCRs [10,13]. That could lead to a long-lasting activation without a regulation by feedback mechanisms, eg receptor down-regulation, affecting negatively to the cardiovascular system [10,13]. Activating AABs against β2ARs are theoretically supposed to increase cardiac and peripheral sympathetic tone and, surprisingly, the prevalence of activating AABs against M2Rs has been implicated to link to tachyarrhythmias, as well [19]. Cardiac sympathetic tone tested with other methods might be normal or even attenuated in NT1 and could not explain the presumed increased risk of cardiovascular diseases in NT1 patients. Our newly found link between activating autonomic AABs and NT1 could be associated with the putative increased cardiovascular morbidity in NT1. But, on the other hand, the existence of these AABs could be secondary to the damage of the autonomic hypocretin pathways seen in NT1 [38]. Still, previously, no aberrations in direct cardiac sympathetic functioning in NT1 were found which indicates that there is no actual sympathetic denervation [37]. Thus, the underlying pathological mechanism between NT1, autonomic symptoms, and alleged cardiovascular morbidity might be in connection with functional activating AABs targeting autonomic nerves.

Further, NT1 patients tend to be overweight [2,3,30] even though they may eat less than peers [39]. The adipose tissue is innervated by both sympathetic and parasympathetic nerves [32]. Sympathetic inputs stimulate lipolysis and parasympathetic tone could promote fat storage [32]. As cholinergic M2Rs are widely expressed in the gastrointestinal system, the discovery of the AABs might be associated with the link between narcolepsy and obesity. On the other hand, hypocretin is involved with various autonomic functions, eg cardiovascular, metabolic, thermo-regulatory, and gastrointestinal regulation, and in food intake [5,27]. Hypocretin

Table 2
Numbers of patients and controls positive for antibodies.

	NT1 (N = 10)	Healthy controls (N = 100)	P
Activating autoantibodies against β2 adrenergic receptors	5/10 (50%)	2/100 (2%)	<0.001
Activating autoantibodies against muscarinic M2 receptors	10/10 (100%)	0/100 (0%)	<0.001
Activating autoantibodies against nociceptin-like receptors	9/10 (90%)	0/100 (0%)	<0.001

Values are numbers of test-positive subjects compared to all the tested subjects, with percentage. Healthy controls are from the previous validation study. P values were computed with Fisher's exact test. NT1: narcolepsy type 1; β2: sympathetic beta 2 adrenergic receptor; M2: parasympathetic muscarinic 2 acetylcholine receptor.

Table 3
Antibody activity.

β2 adrenergic receptor AABs (5/10)	12.5 (4.1)
Muscarinic M2 receptor AABs (10/10)	−15.2 (0.9)
Nociceptin-like receptor AABs (9/10)	19.6 (0.5)

Change in beating frequency (beats/60 s) in the presence of autoantibodies of the patients positive for the autoantibodies. Values are means with standard deviation. NT1: narcolepsy type 1; β2: sympathetic beta 2 adrenergic receptor; AABs: autoantibodies; M2: parasympathetic muscarinic 2 acetylcholine receptor.

deficiency could promote obesity by reducing sympathetic tone and resting metabolic rate [32]. Still, there were no differences in metabolic rate between NT1 patients and controls [32]. Cholinergic dysfunction has been previously implicated in narcolepsy. Cholinergic pathways contribute to REM sleep, arousal, and the maintenance of wakefulness [3], ie all the functions impaired in narcolepsy. Evidence of functional cholinergic AABs were found in a group of patients with narcolepsy consisting of both NT1 and NT2 patients [40], though the exact target of these AABs has not yet been clarified.

As hypocretin neurons are more involved with sympathetic than parasympathetic regulation [4], these reactive changes could affect sympathetic nervous system more, leading to sympathetic dominance and cardiovascular morbidity. Moreover, it is also possible that the supposed cardiovascular comorbidity in the elderly NT1 patients could [40], simply, be due to disorganization of wake and sleep behavior instead of autonomic dysfunction.

Furthermore, these M2R receptor antibodies may, in addition, be associated with cataplexy. Since, in canines, cholinergic M2 stimulation was shown to aggravate cataplexy and M2 blockade suppressed it [41]. There are autonomic alterations during cataplexy [42]. It was associated with a significant increase in muscle sympathetic nerve activity (MSNA) and BP, while HR decreased [42]. No significant autonomic changes were seen before the start of a cataplectic attack [42]. This may indicate that the autonomic nervous system alterations and cataplexy are activated simultaneously in a cortical level [42], and it is possible that this is related to the activating M2 AABs.

It is approximated that up to 85% of NT1 patients suffer from chronic pain [6]. Nociception and pain are regulated by hypocretin-1 in the central and peripheral nervous system [6]. In our study, most of the NT1 patients were positive for activating AABs against nociception receptors. Thus, there might be an association with NT1 and altered pain sensation and these AABs against nociception receptors reinforce this link.

It is possible that the emergence of these activating autoantibodies is reactive - and secondary - to the loss of hypocretin neurons instead of being an independent pathological factor. In the light of current knowledge, the hypocretin cell destruction in NT1 is T-cell mediated and, moreover, no clear evidence of pathogenic autoantibodies have been detected [39,43] Even if these antibodies are not explanatory factors for the symptoms of narcolepsy patients, they are at least potential markers of the involvement of these autonomic and nociception pathways in the symptoms of narcolepsy.

Sleep-related hallucinations are common in narcolepsy [2,44]. The hallucinations may be visual, auditory, or tactile, and can occur while falling asleep or waking up [2]. In addition, there are cases of comorbid psychosis and NT 1 [45], but the exact prevalence of psychotic disorders in narcolepsy is yet unknown, and, moreover, the hallucinations in NT1 have a different character compared to the hallucinations in schizophrenia [44,46,47]. Muscarinic M2 receptors are involved with dopamine metabolism in the brain: they regulate the release of dopaminergic terminals in the striatum [48,49], and they are densely expressed by the cholinergic neurons in nucleus accumbens [50,51]. In schizophrenia, hallucinations are thought to be caused by a disturbed cortical pathway through the nucleus accumbens, resulting in an increased subcortical release of dopamine and augmenting D2 receptor activity [52]. In humans, dorsal striatum is formed of caudate nucleus and putamen, and the ventral striatum consists of the nucleus accumbens and the striatal portion of the olfactory tubercle, inter alia [51]. The neurophysiological basis of the hallucinations in narcolepsy has to date been unresolved. Hallucinations are somewhat rare symptoms in diseases of the brain in general, but particularly common in narcolepsy. The existence of the activating M2 AABs could suggest that the cholinergic pathways in nucleus accumbens might be involved in the emergence of hallucinations in narcolepsy patients. It could even be hypothesized that the activating AABs against M2Rs could affect the cholinergic neurons in the nucleus accumbens leading to the hallucinations in narcolepsy or be a marker of involvement of these pathways in NT1. Perhaps these M2R antibodies are not only related to the symptoms of the autonomic nervous system in NT1, but additionally to the psychiatric problems due to their abundant presence in the brain. In addition, other psychiatric disturbances than hallucinations are more frequent in NT1 patients than among the general population [2]. Hypocretin is linking emotional stress to autonomic functions [53] and, of course, affecting the situation and causing symptoms of anxiety and even depression.

4.1. Limitations

Some limitations of the study need to be acknowledged. The sample size of the tested NT1 patients was quite small, and, what is more, there was no matched control group. Since the controls were not matched, it is possible that the high rate of positive responses among NT1 patients could be due to technical variability in the assay system or there might even be a shift in the number of positive samples in the population level. In addition, the subjects in the used reference dataset had not been routinely investigated for NT1; still, it would be extremely unlikely for them to have NT1 because none of them had any symptoms indicating it. The results in this study are preliminary and they should be confirmed in a larger case−control study.

Further, the method we used is very laborious and time-consuming compared to ELISA, also a common method used to

analyze GPCR AABs. ELISA could perhaps be used in the future for routine clinical practice. However, the ELISA method cannot distinguish between functional and inactive GPCR AABs, as can the method we used [13].

4.2. Strengths

Our study has certain strengths. This is the first time activating AABs against β2AR, M2R, and nociception receptors have ever been measured in NT1 patients. The diagnoses of NT1 in all the patients were confirmed by CSF hypocretin measurement and there were no possibilities of misdiagnosis.

5. Conclusions

NT1 patients harbored activating autoantibodies against M2Rs, β2ARs, and nociception receptors. The finding brings more information about the connection between NT1, autonomic complaints, hallucinations, and pain, and might be secondary to the impairment of the hypocretin pathways.

Financial disclosure

MO has received working grants from Alfred Kordelin Fund for General Development and Education sr and Suomen Unitutkimusseura. EP, GW, AA, and MP declare that they have received no financial support for the study.

Non-financial disclosure

None.

CRediT authorship contribution statement

Maija Orjatsalo: Conceptualization, Formal analysis, Writing - original draft. **Eemil Partinen:** Conceptualization, Writing - review & editing. **Gerd Wallukat:** Investigation, Writing - review & editing. **Anniina Alakuijala:** Conceptualization, Writing - review & editing. **Markku Partinen:** Conceptualization, Writing - review & editing.

Acknowledgements

We thank Anne Huutoniemi for the valuable help in organizing and collecting data.

Abbreviations

β2AR	β2 adrenergic receptor
AASM	American Academy of Sleep Medicine
AAB	Autoantibody
BMI	Body mass index
BP	Blood pressure
CSF	cerebrospinal fluid
ESS	Epworth Sleepiness Scale
GPCR	G protein-coupled receptor
HR	Heart rate
ICSD 3	International Classification of Sleep Disorders Version 3
M2R	M2 muscarinic acetylcholine receptor
^{123}I-MIBG	^{123}I-Meta-iodobenzylguanidine
NT1	Narcolepsy type 1
NT2	Narcolepsy type 2
REM	Rapid eye movement

Conflict of interest

None.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2020.11.038.

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