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Case Report

Recurrent hypersomnia: Report of medication-responsive cases

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ABSTRACT

Introduction: Recurrent hypersomnia (RH) is a rare disorder without established treatment.
Methods: We report 2 RH medication-responsive cases with typical characteristics of Kleine–Levin syndrome (KLS).
Case-reports: A 10 y.o. girl and a 14 y.o. boy presented with sudden sleepiness for 3–9 days (every 2–3 weeks). Physical examination, brain images and blood tests were normal. Polysomnographic findings were heterogenous, including disrupted sleep architecture. MSLTs revealed 2–3 SOREMPs and short sleep latency. Carbamazepine rendered girl's sleep normalization, while risperidone normalized boy's sleep cycles.
Conclusions: Facing the absence of clinical trials in RH, reports of responsive cases are the available therapeutic evidence.

1. Introduction

Recurrent hypersomnia (RH) is a rare disorder that generally affects teenagers and is characterized by episodes of excessive sleep lasting up to several days, when patients sleep almost all day and rise only to eat and void. When associated with behavioral or cognitive disturbances, compulsive eating and hypersexuality it is called Kleine–Levin syndrome (KLS) [1–3].

Due to its distinctive clinical characteristics, KLS is usually differentiated from other causes of hypersomnolence, like narcolepsy, idiopathic hypersomnia and depression, but polysomnography is required for excluding sleep disorder breathing [3]. Neuroimage and other ancillary tests may be necessary for assessing other clinical and neurological conditions.

The cause of KLS is not established, but autoimmune and genetic factors are suspected [4–6]. Infections, fever, trauma,

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and stress may trigger the disease. Although clinical and neurophysiological aspects have already been characterized [1–3,7], the pathophysiology of KLS is still obscure. Hypothalamic dysfunction was suggested because of the findings of low hypocretin-1 levels in central system fluid (CSF) during symptomatic episodes [8] and decreased thalamic blood flow demonstrated during sleep attacks [9], although thalamic [10] and widespread brain hypermetabolism were recently described [11].

There is no clinical trial evaluating drugs for the treatment of RH [12]. The only available therapeutic evidence is obtained from case reports and series of cases [1,2,5,13–16]. In this setting, we report the cases of RH patients with typical characteristics of KLS, with a complete and sustained response to pharmacological treatment.

2. Methods

Two RH patients who are accompanied for years by the same physician (CMF), in Passo Fundo – RS, Brazil, have their cases reported. The written consent was previously obtained from patients for publication purpose.

2.1. *Case reports*

- Case 1: a 10 y.o. Afro-Brazilian girl began with sudden sleepiness that lasted 7 days, when she woke for only 1 h a day, with confusion and greedy hunger. The attacks recurred every 2 weeks, resulting in weight gain. Between the attacks she slept normally and forgot the episodes. Physical examination, brain MRI, EEG, CSF and blood tests were normal. The polysomnography and multiple sleep latency test (MSLT) findings are summarized in Table 1. She underwent use of antidepressants, lithium, and thioridazine without success. Carbamazepine up to 1200 mg/day rendered the normalization of sleep. Attempts of dose reduction resulted in attacks (the last in 2013). Nowadays she is 23 y.o.

Table 1 – Neurophysiological characteristics of the cases (during sleep attack).

	Case 1	Case 2
Polysomnography		
Efficiency (%)	95	51
Sleep latency (min)	3	5
REM latency (min)	100	71
N1 (%)	2	5.5
N2 (%)	63	50
N3 (%)	13	36
REM (%)	22	8.5
Arousals (per hour)	<10	25
Respiratory events (per hour)	<5	16
MSLT[a]		
Sleep latency (min)	4	2
SOREMPs[b]	3	2

[a] Multiple sleep latency test.
[b] Sleep onset REM period.

- Case 2: a 14 y.o. Caucasian boy had undetermined fever for 7 days. Since then he presented sudden sleepiness for 3–9 days, awakening for 2 h a day with confusion, marked hunger and sexual disinhibition. During intervals he slept normally and remembered the attacks as dreams. Physical examination, brain CT and blood tests were normal. Table 1 shows the polysomnographic and MSLT findings. Treatments with antidepressants, methylphenidate, divalproate and carbamazepine were unsuccessful. Risperidone 1 mg/day decreased the frequency and duration of attacks. With 1.5 mg/day the episodes ceased, except during discontinuation in 2013. He returned to risperidone and is 21 y.o. at present, free of sleep attacks since 2013.

3. Discussion

Due to the rarity of RH, there are no trials providing therapeutic guides [12]. Treatment evidence is based on empirical use provided by case reports and series of cases. Carbamazepine [5,13], valproic acid [14], antipsychotics [1], lithium [1,2], amphetamines [1], acetazolamide [15], and clarithromycin [16] are the drugs that were described to be helpful for normalizing sleep cycles in cases of KLS. When clearly menstrual-related, RH may also be treated with oral contraceptives [5].

The heterogeneity of response to medications is remarkable from the reports, because no specific drug obtains success in more than circa 40% of cases [1]. This suggests that the mechanisms underlying RH are complex and that hypothalamic dysfunction may be an epiphenomenon, part of a process generated by processes affecting more widespread central neurotransmission [11]. In this setting, the assessment of HLA-DQB1*0602 and of CSF hypocretin levels in all RH patients would be an interesting endeavor in terms of physiopathologic investigation [4,8]. However, these analyses are not ordinarily performed due to logistical unavailability.

An interesting issue regarding our reported cases is the fact that MSLT accomplished during the sleep attacks revealed at least two sleep onset REM periods (SOREMPs) and very short sleep latency, suggesting that these findings are not pathognomonic of narcolepsy, as previously stated [17,18].

The prognosis of RH, especially of KLS, is not as benign as previously stated [3]. This reinforces the necessity of more studies devoted to RH, not only for the elucidation of its physiopathology, but also for guiding specific therapeutic strategies.

Acknowledgments and disclosure of interests

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