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CASE REPORT

Orgasmolepsy in Narcolepsy Type 1 Responsive to Pitolisant: A Case Report

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Abstract: We describe a case of a young male patient with narcolepsy type 1 (NT1), who developed generalized cataplexy attacks during sexual intercourses, on which we have obtained a satisfactory control with pitolisant. Orgasmolepsy is an uncommon feature of NT1 that has been poorly described in the literature. The prevalence of this condition is unclear, as it is reasonably underreported by patients for embarrassment and not well investigated by physicians. Pitolisant is a novel treatment for narcolepsy, effective on excessive daytime sleepiness and cataplexy by modulating the histaminergic system. Real-world data collection on pitolisant efficacy and safety is still ongoing. However, pitolisant effectiveness on orgasmolepsy in NT1 has no precedent in the literature. Orgasmolepsy and other sexual disturbances should be actively searched in narcoleptic patients and, if present, may guide clinicians to prefer pitolisant or sodium oxybate, avoiding antidepressants for their possible sexual side effects.

Keywords: NT1, cataplexy, sexual dysfunction, narcolepsy treatment

Introduction

Narcolepsy is a chronic, disabling sleep-wake disorder characterized by excessive daytime sleepiness (EDS), cataplexy, hypnagogic-hypnopompic hallucinations, sleep paralysis, impaired nocturnal sleep and automatic behaviors. These features may be differently combined in narcolepsy type 1 (NT1, with cataplexy) and type 2 (NT2, without cataplexy), with high variability in the clinical presentation of the disease.[1,2] Often unrecognized and diagnosed late, narcolepsy is a rare disorder with an estimated prevalence of 20–50/100.000.[3]

The diagnosis of NT1 is suspected on the basis of patient medical history and confirmed by night polysomnography (PSG) followed by multiple sleep latency test (MSLT) and/or hypocretin-1 deficiency (≤110 pg/mL) in the cerebrospinal fluid (CSF). Additionally, the human leukocyte antigen (HLA) class II HLA-DQB1*0602 allele is found in the 98% of patients with NT1.[1,2]

Modafinil, armodafinil and solriamfetol are first-line treatments for EDS. Sodium oxybate is effective on EDS, cataplexy and fragmented nocturnal sleep, while antidepressants are primarily used for cataplexy.[2] Pitolisant is a histamine H_3 receptor antagonist/inverse agonist, approved in 2016 by the European Medicines Agency (EMA) as a first-line treatment for both EDS and cataplexy. In 2019, it has received the approval of the US Food and Drug Administration (FDA) for the treatment of EDS in narcolepsy, while the indication for cataplexy is currently under review.[2,4]

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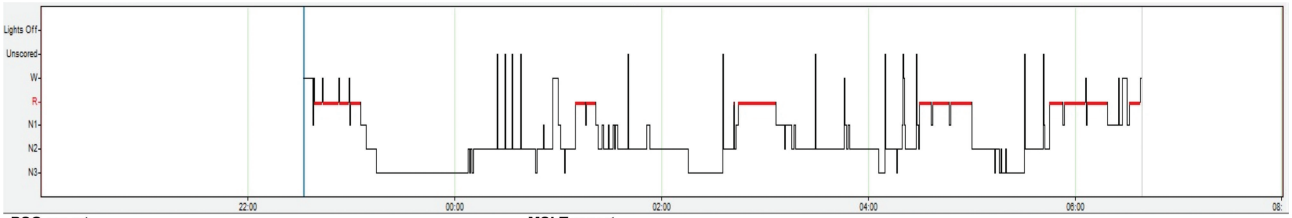
The loss of orexin neurons in the lateral hypothalamus, probably mediated by autoimmune mechanisms, plays a key role in the pathophysiology of NT1.[2] Hypocretin is actively involved in the regulation of the dopaminergic system, which is crucial for motor control, but also in promoting wakefulness, in sexual behavior and reward mechanism.[2,5] Hypocretin deficiency facilitates the transient emotion-triggered muscle atonia of cataplexy, due to dysfunctional hypothalamus-amygdala-brainstem interactions.[4,6]

Several sexual disorders may be associated with narcolepsy. Hypnagogic hallucinations may present as complex and multi-modal experiences with sexual content, which may occur at night and during daytime sleepiness moments. Hallucinatory episodes of sexual activity combined with out-of-body experiences, sexual assaults and extramarital affairs leading to social and legal conflicts have been described.[7,8] In such cases, a comprehensive clinical evaluation is recommended to distinguish between narcolepsy and psychosis. In addition, cataplexy in NT1 may occur during sexual intercourses facilitated by the emotional trigger. This phenomenon was defined "orgasmolepsy" by Jakob Rothfeld, who described it for the first time in 1928.[9] This embarrassing sexual feature of narcolepsy may significantly impact on patient's relational and affective life. However, it is so far poorly characterized, as it has been infrequently reported in the literature.

Case Report

A 26-year-old man developed EDS and partial cataplexy attacks at the age of 13. He arrived to our Sleep Medicine Center (Clinical Neurology Unit, Udine University Hospital, Italy) at the age of 15, by presenting irrepressible need to sleep with an Epworth Sleepiness Scale (ESS) score of 14, and sporadic partial cataplexy attacks with sagging of facial muscles and head drooping triggered by emotions, lasting a few seconds. Tested with night PSG, the patient showed a sleep latency of 6.0 minutes with a Rapid Eye Movement (REM) sleep latency of 1.0 minute. The MSLT revealed a mean sleep latency of 3.2 minutes and Sleep Onset Rapid Eye Movement Periods (SOREMPs) in five tests out of five (Figure 1). Since diagnostic criteria for NT1 were fulfilled, CSF hypocretin level was not assessed. Furthermore, he tested positive for HLA-DQB1*0602. The patient was initially treated with modafinil 200 mg/day, titrated up to 300 mg at the age of 19, with satisfactory control on EDS, and ESS scores persistently under 10 at follow-up. An add-on treatment with venlafaxine for cataplexy was initially considered, but eventually discarded due to the poor clinical relevance of cataplectic manifestations.

At the age of 23, the patient reported a major impairment in daytime sleepiness related to a higher workload, with an ESS score of 15. At the same time, he also started to have cataplexy attacks during sexual intercourses, which had previously occurred normally. Muscle atonia was generalized, lasting 8–10 seconds in proximity of climax, being more intense during the first orgasm in case of multiple orgasms within the same intercourse. He initially avoided mentioning this problem throughout the follow-up visits. Given the worsening of EDS, however, we introduced pitolisant 4.5 mg/day as an add-on treatment with modafinil. It was titrated up to 18 mg/day in four weeks, obtaining a moderate reduction of EDS (ESS



PSG report		MSLT report	
Sleep latency (min)	6	Mean sleep latency (min)	3.2
REM sleep latency (min)	1	SOREMPs	5/5
Total sleep time (min)	470		
Number of awakenings	3		
Wake after sleep onset (min)	10		
Sleep efficiency (%)	97		

Sleep stages		Nap session	(time)	SL (min)	RL (min)
Stage W (%)	2	I	(10.00 a.m.)	3.5	4
Stage N1 (%)	8	II	(12.00 p.m.)	3	3.5
Stage N2 (%)	44	III	(2.00 p.m.)	1	2.5
Stage N3 (%)	19	IV	(4.00 p.m.)	6.5	3
Stage R (%)	26	V	(6.00 p.m.)	2	4

Figure 1 Patient hypnogram, night PSG and MSLT findings at the time of diagnosis.
Abbreviations: PSG, polysomnography; MSLT, multiple sleep latency test; REM, rapid eye movement; SOREMPs, sleep-onset REM periods; W, wakefulness; N1, NREM1 stage; N2, NREM2 stage; N3, NREM3 stage; R, REM stage; min, minutes.

score 12) and the resolution of partial cataplexy attacks. He continued to increase the dosage by 4.5 mg weekly. At a dose of 27 mg/day, he noticed a significant improvement of generalized cataplexy during sexual activity and, for the first time, he informed us of his sexual disturbance. Although orgasmolepsy was still occurring within each intercourse, muscle atonia became milder, sparing the lower limbs and lasting 2–3 seconds.

At that dosage, however, the patient developed three attacks of migraine with aura in two weeks, each one occurring 1.5–2 hours after pitolisant intake. Following these episodes, he informed us about his personal and familial medical history of migraine; he had previously experienced rare attacks of aura without migraine, and his mother is affected by migraine with aura as well. Pitolisant reduction to 18 mg/day prevented other migraine attacks, but led to an unsatisfactory control of orgasmolepsy again.

Discussion

Cataplexy triggered by emotions during sexual intercourses, formerly known as orgasmolepsy, is a rare manifestation of cataplexy in NT1 that has received poor attention in the literature. Aside from a few reports,[10,11] a case series by Poryazova et al is the only study published in the last two decades evaluating features and prevalence of orgasmolepsy in NT1.[5] As observed in our patient, orgasmolepsy typically occurs at each sexual intercourse. Muscle atonia is often generalized in body distribution and more pronounced in case of emotional involvement. Poryazova et al described only three patients with orgasmolepsy in a series of 29 with NT1. Two of them were effectively treated for cataplexy with sodium oxybate, but orgasmolepsy improved only in one case.[5] Differently, our patient was effectively treated with pitolisant.

A few clarifications on the relationship between sexual disorders and drugs used for narcolepsy should be made. Firstly, increased and decreased libido are both reported as uncommon adverse events of pitolisant;[12] decreased libido is also an uncommon side effect of modafinil.[13] Secondly, all antidepressants used to treat cataplexy in patients with NT1 are known to be associated with decreased libido, erectile dysfunction, delayed orgasm or anorgasmia and delayed ejaculation.[14] Moreover, cataplexy, which has been described as an adverse reaction to modafinil in a patient without narcolepsy,[15] has also been reported as an uncommon side effect of pitolisant.[12] In our case, the patient has never reported changes in his sexual drive; partial cataplexy was already present when he started the treatment with modafinil and it remained unchanged for several years; orgasmolepsy appeared at a time of global worsening of the disease; finally, he clearly showed a dose-related response on both partial cataplexy and orgasmolepsy with pitolisant.

Pitolisant is an H_3 receptor antagonist/inverse agonist effective on EDS and cataplexy.[4,16] H_3 receptors are highly expressed in the amygdala, a region strongly involved in cataplexy induction. The amygdala is modulated by histaminergic neurons of the tuberomammillary nucleus, which are almost doubled in NT1, probably in response to the loss of orexin neurons.[4,16] It has been hypothesized that orgasmolepsy may be associated with persisting amygdala firing during intercourses and resultant disinhibition of brainstem atonia-generating neurons.[5] Pitolisant effectiveness on cataplexy and orgasmolepsy, therefore, may be related to the stimulation of histaminergic neurons in the tuberomammillary nucleus, with consequent amygdala inhibition.

According to the limited data available in the literature, prevalence of orgasmolepsy varies between 10% and 31% of NT1 patients,[5] although it would be expected to be more frequent, considering the strong emotional content of sexual intercourse. Several explanations are possible for this discrepancy: sexual dysfunction could be unreported for embarrassment (our patient reported his disturbance only after it was improved by pitolisant); given the age of onset of narcolepsy, active sexual life may start when effective treatments for cataplexy are already ongoing, preventing orgasmolepsy. Finally, orgasmolepsy might be concealed by other sexual disorders, which frequently occur among NT1 patients as part of a dysautonomic syndrome, particularly erectile dysfunction in 48% of men and vaginal dryness in 81% of women.[17]

We emphasize the importance of actively searching for sexual disturbances in patients with narcolepsy, because these represent limiting factors in their relational life. As we reported above, sexual disorders may be related to medications used for narcolepsy or to the disease itself, as in the case of orgasmolepsy. Such information may help to clarify data on prevalence and features of this condition and should guide clinicians in the choice of an appropriate treatment for cataplexy in NT1. We suggest to prefer pitolisant or sodium oxybate in narcoleptic patients with orgasmolepsy or other sexual disorders, particularly avoiding antidepressants for their common sexual side effects.

Ethical Standard Statement

This study followed the tenets of the Declaration of Helsinki and was performed according to the guidelines

of the Institutional Review Board of University of Udine Medical School. The patient's written consent was obtained for publication of this report.

Author Contributions

All authors have seen and approved the manuscript.

Disclosure

The authors report no conflicts of interest.

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