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CASE REPORT

Vortioxetine Effects on Sleep Architecture in Treatment of Comorbid Depression in Adolescent Patient with Narcolepsy and Cataplexy

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Abstract

This report presents a rare case of adolescent patient treated by novel antidepressant vortioxetine for depressive disorder comorbid to narcolepsy type 1 (NT1) and newly diagnosed REM behavior disorder (RBD) and describes the overall clinical improvement of the conditions. Additionally, we discuss effect of vortioxetine on sleep architecture by evaluating objective polysomnographic studies before and on the treatment. We propose a possible efficacy of this multimodal serotoninergic agent in treatment of RBD associated with NT1.

Abbreviations:

AASM	- American Academy of Sleep Medicine
AD	- antidepressant(s)
AHI	- apnoe-hypopnoe index
AI	- arousal index
CGI-S	- Clinical Global Impression Severity Scale
CNS	- central nervous system
CSF	- cerebrospinal fluid
DNS	- disturbed nocturnal sleep
EDS	- excessive daytime sleepiness
EEG	- electroencephalography
ESS	- the Epworth Sleepiness Scale
Hcrt-1	- hypocretin-1
MRI	- magnetic resonance imaging
MSLT	- Multi Sleep Latency Test
NT1	- narcolepsy type 1 (with cataplexy)
PLMI	- periodic limb movements index
RBD	- REM sleep behavior disorder
REM	- rapid eye movements
REML	- REM sleep latency
RWA	- REM sleep without atonia
SE	- sleep efficiency
SOL	- sleep onset latency
SOREMP	- sleep onset REM sleep periods
TST	- total sleep time
VOR	- vortioxetine
vPSG	- video-polysomnography
WASO	- wake after sleep onset
5-HT	- serotonin (receptor)

INTRODUCTION

Depressive disorder has several overlapping symptoms with narcolepsy including sadness, pessimism, low self-esteem, worsening of cognitive performance and psychosocial functioning, disrupted nocturnal sleep (DNS) and daytime fatigue (Findling *et al.* 2018). A recent meta-analysis (Li *et al.* 2020) reported prevalence up to 32% of comorbid depressive symptoms in patients with narcolepsy across all age groups. By the deficit of hypocretin-1 (hcrt-1) induced cholinergic-monoaminergic signalization dysbalance model and hypoactivity of reward pathways is similar to those in patients with unipolar major depressive disorder and have been proposed for further investigation (Li *et al.* 2020; Mahoney *et al.* 2019).

The aim of this case report is to share the experience with first-time use of antidepressant (AD) vortioxetine (VOR) in depressive adolescent patient with NT1 and to objectively assess its impact on sleep structure by means of polysomnography. To the best of our knowledge, this application has not been previously described in literature, with lacking information about VOR´s efficacy on narcolepsy presentation and coexisting depression, particularly in adolescence.

REPORT OF CASE

We describe a case of 15-years old male patient presented with excessive daytime sleepiness (EDS), cataplexy, hypnagogic and hypnopompic hallucinations, depressive mood prone to dysphoria, hypohedonia, psychomotoric inhibition and bradyphrenia. Patient´s parents observed significant behavioral problems (non-compliance to sleep schedule, autoaggressive and heteroaggressive behavior), psychosocial worsening (social isolation, impairment of school performance and attendance) and apathy for previous 3 months. This patient was having fragmented non-refreshing nocturnal sleep, frequent imperative daytime sleep attacks (lasting 10-15 min) accompanied by vivid visual and tactile sleep hallucinations (e.g. microzooptic, sensations of touching, tingling, etc.) which started approx. three years ago prior to diagnosis of NT1. He was experiencing sporadic cataplectic attacks few times per month triggered by positive and negative emotions (presented predominantly as head falling to the side with weakening of facial and neck muscles, usually without loss of postural muscle tone).

The patient´s medical history included borderline hypertrophic cardiomyopathy and arterial hypertension (treated by bisoprolol 2.5 mg/day). The patient was overweight (BMI 26 kg/m2). He was also diagnosed with atopic dermatitis and chronic hypertrophic rhinitis. Magnetic resonance imaging (MRI) of the brain showed slight asymmetry of the right lateral ventricle considered as an anatomic variant and electroencephalography (EEG) depicted generalized slowing of basic EEG activity (slow alpha rhythm 7-8 Hz) with no epileptiform patterns. Laboratory analysis of his cerebrospinal fluid (CSF) excluded neuroinfection or autoimmune encephalitis. There were no clinical signs of endocrinophaties, congenital metabolic and genetic disorders. The patient was found DQB1*06:02 allele positive and with low levels of hcrt-1 in CSF (< 20 pg/ml), which together with Multi Sleep Latency test (MSLT) positivity (4 of 5 sleep onset REM periods (SOREMPs), average sleep onset latency 1.50 min and average REM sleep latency 3.15 min) and clinical symptoms testified for the diagnosis of NT1. The patient´s Epworth Sleepiness Scale (ESS) score was 13 of 24.

He was managed in the specialized Centre for Narcolepsy with no adequate response to methylphenidate 18 mg/day treatment and with history of transiet use of selective serotonin reuptake inhibitors (SSRI) AD (fluoxetine 20 mg/day; sertraline 50 mg/day), before hospitalization at Clinic of Psychiatry was indicated by outpatient pedopsychiatrist. He was diagnosed with episode of atypical depression after clinical assesment completed by Clinical Global Impression - Severity scale (CGI-S) with score 6 of 7 points. Patient was prescribed with the mutlimodal serotoninergic AD vortioxetine because of its better safety and tolerability in pediatric population (Findling *et al.* 2018) regarding the patient´s cardiovascular condition.

After initiation of VOR in dose 20 mg/day to treat comorbid depression, decrease of EDS (the ESS downscaled from 13 to 9 points), fatique, sleep-related hallucinations, reduction of cataplectic events and mood improvement were clinically observed. The CGI-S score improved from 6 to 4 and the Clinical Global Impression-Improvement (CGI-I) score was 2. Eventually, the patient responded to 13 days of pharmacologic treatment by reducing both symptoms of narcolepsy and depression supported by compliance to narcoleptic regimen (a scheduled afternoon nap). After a week, a shift to hypomania was noticed, so an antipsychotic (olanzapine 2.5 mg/day) was added for mood stabilization. The initial diagnosis of atypical depressive episode was re-evaluated.

The patient underwent polysomnographic study. The written informed consent was obtained from the parents and the assent from the patient. Both sleep studies were conducted via Philips SleepwareG3 at Clinic of Psychiatry in Martin University Hospital and scored manually by two scorers according to the American Academy of Sleep Medicine (AASM) manual (Berry *et al.* 2017).

There were two standard attended overnight video-polysomnographies (vPSG) recorded with following outcomes (see Table 1). In the first sleep study (PSG I) on medication-free patient, the disturbances of sleep continuity, with frequent arousals (arousal index, AI 26.9) and increased wake after sleep onset (WASO 92.5 min) were noticeable, leading to decreased sleep efficiency (SE 78.3%). The mentioned DNS parameters,

together with higher portion of N1 sleep stage (N1 26.2%), were quite characteristic for pediatric patients with narcolepsy (Bassetti *et al.* 2019, Maski *et al.* 2020). REM latency (REML 91.0 min) did not meet the criteria of nocturnal SOREMP (nSOREMP < 15 min from sleep onset on overnight PSG) which represents one of the specific diagnostic biomarkers of NT1 (Bassetti *et al.* 2019, Maski *et al.* 2020). There were no signs of periodic limb movements syndrome or sleep related breathing disorders. On the following PSG night (PSG II), when patient received VOR in dose 20 mg/day for almost two weeks, the mentioned sleep parameters AI and WASO increased and SE was reduced (to 71.2%). Stage N1 duration decreased (N1 11.7%) and stage N2 increased (N2 47.1%) compared to PSG I. REM latency time almost doubled (REML 167.5 min) which might be the possible effect of the AD on REM sleep. There was no overall supression of REM sleep duration (REM sleep 23.5%), except for less frequent REM to Wake transitions observed (see Figure 1b) compared to hypnogram of PSG I (see Figure 1a), which might be the reason for reduced frequency of sleep associated hallucinations during PSG II. Video recording during vPSG I inidicated diminished physiologic atonia during REM sleep by the evidence of dream-enacting behavior (represented by non-violent stretching movements of upper limbs, with no vocalizations). Evaluation of REM sleep without atonia (RWA) was subsequently manually performed regarding the AASM manual (Berry *et al.* 2017) criteria to score tonic and phasic muscle activity during REM sleep. There was no visual evidence of RBD during vPSG II compared to vPSG I and nRWA index significantly decreased (from 46.67% to 14.5%).

Tab. 1. Data results of two attended polysomnographic nights (PSG I/PSG II)

	PSG I	PSG II
Total recording time (min)	480.2	560.5
Time in bed (min)	471.9	534.8
Sleep period time (min)	462.2	533
Total sleep time (min)	369.7	381
% Sleep efficiency	78.3	71.2
Sleep onset latency (min)	9.7	1.3
Wake after sleep onset (min)	92.5	152.5
Arousal index	26.9/hTST	27.8/hTST
N1 (%)	97 (26.2)	44.5 (11.7)
N2 (%)	122 (33)	179.5 (47.1)
N3 (%)	65 (17.6)	67.5 (17.7)
REM (%)	85.7 (23.2)	89.5 (23.5)
REM latency (min)	91	167.5
PLMI	1.2	4.8
AHI	0.0	0.0
Total tonic REM sleep index (%)	15.8	10.6
Total phasic REM sleep index (%)	30.9	3.9
nRWA index (%)	46.7	14.5

AHI – apnoe-hypopnoe index ; nRWA- nocturnal REM sleep without atonia index; PSG - polysomnography; PLMI – periodic limb movements index; TST – total sleep time

DISCUSSION

The uniqueness of this study lies in the fact that VOR has not been researched yet in the context of NT1 and comorbid depressive disorder, nor by the utilization of objective sleep study. Our PSG findings revealed that REM sleep latency was significantly delayed (with no change in total duration of REM sleep), decreased duration of N1 stage (inconsistently with the previous study (Wilson *et al.* 2015) of VOR´s effect on sleep structure) and eventually increased WASO in the reported case while taking VOR. In contrast to sleep fragmentation caused by VOR (with even lower SE% than formerly), the overall clinical condition improvement was remarkable.

Most of the AD, by their mechanisms of selective monoaminergic reuptake inhibition and anticholinergic REM suppression, ensure improvement of cataplexy (which is believed to be REM sleep atonia intrusion into wakefulness) (Bassetti *et al.* 2019; Morse, 2019; Thorpy & Bogan, 2020). Vortioxetine as a novel multimodal serotoninergic AD is acting as 5-HT1A receptor agonist, 5-HT3, 5-HT7, and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, and 5-HT transporter inhibitor (Findling *et al.* 2018; Wilson *et al.* 2015). It has been suggested that VOR suppresses REM sleep (by increasing REM sleep latency and decreasing proportion of REM sleep), increases duration of sleep stage N1 and decreases total sleep time (TST) assessed by polysomnography in healthy subjects (Wilson *et al.* 2015). Furthermore, the AD has been evaluated as clinically effective in treatment of depression and anxiety in childhood (Findling *et al.* 2018), with a beneficial pro-cognitive effect proofed in animal models and some clinical trials (Frampton, 2016) so far investigated only in adult patients.

During vPSG I recording in drug-naïve patient there was a visual record of dream enactment behavior in REM sleep which together with nocturnal REM atonia index (nRWA index 46.67%) was favorable for the diagnosis of RBD. nRWA index was calculated as the total number of stage R sleep 30-second epochs with RWA (tonic and phasic) to the total number of stage R sleep epochs on the PSG x 100, also the indices were calculated separately for phasic and tonic REM sleep activity (see Table 1). The nRWA index with the cutoff of value ≥ 8% provides diagnostic biomarker of pediatric narcolepsy with great specificity (95.7%) and poor sensitivity (52.9%) (Bin-Hasan *et al.* 2020). Many patients with narcolepsy experience RBD (with prevalence almost 30% in pediatric narcolepsy) (Antelmi *et al.* 2020)

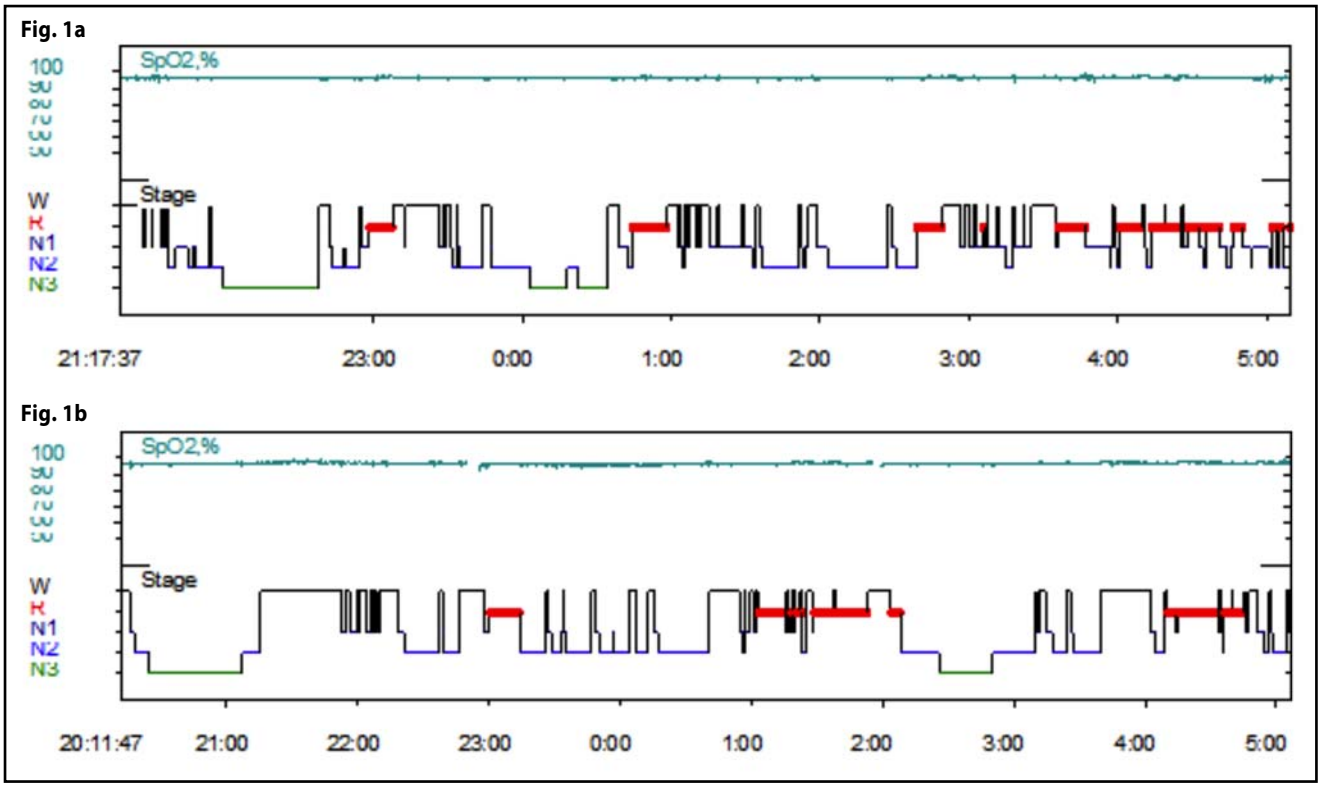

Fig. 1. Hypnogram of PSG I (Fig. 1a) – showing a sleep structure of non-medicated patient; Hypnogram of PSG II (Fig. 1b) – showing sleep structure after almost 2-weeks of treatment by novel antidepressant vortioxetine

which is a REM sleep parasomnia characterized by loss of muscle atonia (RWA represents the neurophysiologic hallmark of RBD) and complex motor behaviors and/or vocalizations (Bassetti *et al.* 2019). RBD is rarely every night phenomenon, but occurs few times per month making it hard to detect without combination of objective and subjective sleep measures (Bassetti *et al.* 2019; Antelmi *et al.* 2020). Abnormal motor dream acting of delicate non-violent pattern was observed during vPSG I in the second half of the night (with no previous reports from the parents) and was not present during vPSG II. This finding is consistent with previous statements that narcolepsy-associated RBD presents more like discreet and non-violent ´pantomime-like´ motor activity (representing intrinsic motor dyscontrol during REM sleep) than in idiopathic RBD phenotype (with no direct link to hcrt-1 levels in CSF) (Antelmi *et al.* 2020). Moreover, motor activity during sleep can be enhanced by other serotoninergic agents (SSRI or venlafaxine) used to manage cataplexy and depression, lately pointed at AD induced RBD (Thorpy & Bogan, 2020). There is only one case report (Du *et al.* 2020) up to date to present VOR as efficient for treatment of RBD in an adult, potentially through the activation of 5-HT1A receptor. In presented case, there was a distinct reduction of RWA activity (nRWA index from 46.7 to 14.5 %), especially phasic activity (from 30.9 to 3.9 %), with no REM behavior episodes recorded during vPSG II, which seems to be the result of the current action of VOR.

Since the narcolepsy and depressive disorder share common cholinergic-monoaminergic signalization dysbalance leading to REM sleep disinhibition, the diagnostic should be appropriate and based on characteristic clinical and PSG findings. In this context, the potential patomechanisms of both coexisting neuropsychiatric disorders with multifaceted clinical presentation in childhood and adolescence should be studied more carefully to select the most suitable treatment approach. Although clinical studies suggest positive results in the treatment of depression by VOR in adolescents (Findling *et al.* 2018), there is still not sufficient evidence of sleep normalization and not even possible link between sleep quality and reduction of depressive symptoms in narcoleptic patients treated by this multi-target AD.

The relevant contribution of this case is to report the experience with the use of VOR in treatment of depressive adolescent patient with narcolepsy and cataplexy pointing to possible beneficial effect on depressive symptoms, narcolepsy daytime symptoms and even on RWA activity. Further research of well-designed double blind randomized studies based on longitudinal monitoring is required to consider VOR to be a potent drug for treating narcolepsy and comorbid depression, respectively to verify its effects on sleep architecture. Regarding the finding of reduced RWA activity, we suggest more studies to explore this clinical benefit, especially in narcolepsy-related RBD of adolescent patients.

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DISCLOSURE STATEMENT

The authors report no financial conflicts of interests.

AUTHORS CONTRIBUTIONS

P.H., M.K., A.H. examined the patient, performed polysomnographic studies. Z.M. and R.V. scored polysomnographic outcomes, analyzed data, wrote the manuscript; I.T. and I.O. managed the patient, contributed to the conception and designed study, supervised the process and revised the paper; K.S.: consulted study findings, supervised and revised the paper. All authors read and approved the final manuscript.

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