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Original Article

Sleep disorders in NiemannPick disease type C, beyond cataplexy

Deborah Moreira Rangel [a, b], Manoel Alves Sobreira-Neto [a, c, f], Camila Rodrigues Nepomuceno [d], Erlane Ribeiro Marques [e, f], Pedro Braga-Neto [a, b, d, *]

[a] Division of Neurology, Department of Clinical Medicine, Universidade Federal do Ceará, Brazil
[b] Neurology Service, Hospital Geral de Fortaleza, Fortaleza, Ceará, Brazil
[c] Universidade de Fortaleza, Fortaleza, Ceará, Brazil
[d] Center of Health Sciences, Universidade Estadual do Ceará, Fortaleza, Ceará, Brazil
[e] Hospital Infantl Albert Sabin, Fortaleza, Ceará, Brazil
[f] Unichristus University, Fortaleza, Ceará, Brazil

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ABSTRACT

Purpose: The aim of this study was to clinically characterize sleep disorders in a cohort of Niemann-Pick type C (NPC) patients, correlating these findings with disease features and polysomnographic (PSG) results.
Methods: We evaluated eight consecutive patients with molecular confirmation of NPC followed at the Hospital Geral de Fortaleza. Patients underwent a comprehensive neurological and sleep evaluation. Four participants underwent polysomnography and then performed the multiple sleep latency test.
Results: All eight patients evaluated had sleep disorders. Four participants performed polysomnography followed by multiple sleep latency test. Chronic insomnia and Obstructive Sleep Apnea (OSA) were the most frequent sleep disorders (62,5%). Two patients were diagnosed with Restless Legs Syndrome (RLS) (25%) and two with probable REM sleep behavior disorder (RBD) (25%). All the patients who did polysomnography had reduced and/or disorganized sleep, with reduction on sleep efficiency, total sleep time and REM sleep time.
Conclusion: Our results suggest that sleep abnormalities in Niemann-Pick type C patients may be more prevalent than previously thought.

1. Introduction

Niemann-Pick type C (NPC) is a rare lysosomal storage disease with a recessive pattern of inherence. Clinical presentation is extremely heterogeneous with the disease ranging from neonatal severe form to adult-onset neurodegenerative form. NPC is commonly defined as a neurovisceral condition with important liver and spleen involvement as well as neurologic and psychiatric findings at different times and with independent courses [1].

There are only a few publications investigating the association between NPC and sleep disorders. To the best of our knowledge, only one study performed polysomnography (PSG) with multiple sleep latency test (MSLT), in five NPC patients, but no clinical evaluation by interview and/or sleep scales was conducted [2].

Cataplexy is defined as a brief episode of bilateral loss of muscle tone with preserved consciousness. Gelastic cataplexy is characterized by this loss of tonus when laughing and is commonly described as one of the main features of NPC. This symptom occurs in about 16% of cases, with higher prevalence in the youngest disease forms. Although cataplexy is rare in the adult form of NPC, it is quite specific to the disease [3,4].

The aim of the present study was to clinically characterize sleep disorders in NPC, correlating potential sleep abnormalities with clinical and disease features.

2. Methods

2.1. Population

The sample comprised eight consecutive patients with NPC followed at the Hospital Geral de Fortaleza from December 2016 to September 2017. The NPC diagnosis was confirmed by molecular analysis.

* Corresponding author. Universidade Federal do Ceará, Department of Clinical Medicine, Rua Prof. Costa Mendes, 1608 – 4° andar – Rodolfo Teófilo, Fortaleza, Ceará, Brazil.
E-mail address: pbraganeto@ufc.br (P. Braga-Neto).

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2.2. Clinical evaluation

All patients underwent a comprehensive neurological evaluation. Ataxia severity was evaluated using the Brazilian validated scale for the assessment and rating of ataxia (SARA) [5]. The NPC Disability scale was also applied to grade NPC severity [6]. Cognitive function was evaluated using the Mini-Mental State Examination (MMSE). Body mass index, Mallampati score, and neck circumference measurements were also determined.

NPC categorization was also performed according to age at onset: pre/peri-natal, onset before three months; early-infantile period, three months to two years; late-infantile period, 2–6 years; juvenile (classical), 6–15 years; adolescent and adult, above 15 years [7].

2.3. Sleep evaluation

Clinical evaluation was performed by two neurologists, one of them specialized in sleep medicine, to detect and diagnose sleep disorders according to the International Classification of Sleep Disorders - third edition (ICSD-3). The Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Brazilian Portuguese version of REM sleep behavior disorder screening questionnaire (RBDSQ-BR), International Restless Legs Syndrome Study Group rating scale (IRLSRS) and Brazilian Portuguese version of the Morningness–eveningness Questionnaire (MEQ) of Horne and Östberg were also used to evaluate and/or grade sleep complaints. All questionnaires were performed with the patient and caregiver as cognitive decline could interfere with some answers [8–12]. All patients were invited to undergo polysomnography (PSG) and perform the multiple sleep latency test (MSLT) (Fig. 1).

2.4. Polysomnographic recordings

Polysomnography (PSG) was performed with a digital polygraph (computerized sleep system; Neurosoft). Data were collected using an electroencephalogram (EEG) (according to the International 10–20 System) (Fp1-M1, Fp2-M2, F3-M1, F4-M2, C3-M1, C4-M2, P3-M1, P4-M2, F7-M1, F8-M2, T3-M1, T4-M2, T5-M1, T6-M2, O1-M1, O2-M2, Fz-Cz, Cz-Pz), bilateral electrooculogram (E1-M2, E2-M1), electrocardiogram (modified V2 lead), and surface electromyography of the mental and submental muscles. Surface electrodes were placed on both anterior tibialis, and extensors of the finger muscles.

Digital video, synchronized with the PSG data, was recorded with an infrared camera (Intelbras). Respiration was monitored as follows: airflow was measured by a nasal pressure transducer system and nasal and mouth thermocouple airflow sensor; chest and abdominal efforts were measured by respiratory inductive plethysmography belts; arterial SaO_2 was measured by pulse oximetry; snoring sounds were measured using a snoring microphone; and body position was determined by a sensor.

All of the technical parameters used were determined in accordance with the American Association of Sleep Medicine (AASM) manual for the scoring of sleep and associated events: rules, terminology, and technical specification [13].

The MSLT was conducted on the day following nocturnal PSG. Naps were recorded at 08:00, 10:00, 12:00, 14:00, and 16:00 h. The EEG (F3-A2, F4-A1,C4-A1,C3-A2, O1-A2, O2-A1), horizontal and vertical EOG, and submental EMG were employed for the daytime nap tests [14].

The diagnosis of sleep disorders was performed according to the International Classification of Sleep Disorders – third edition (ICSD-3), using clinical, PSG and MSLT information [15].

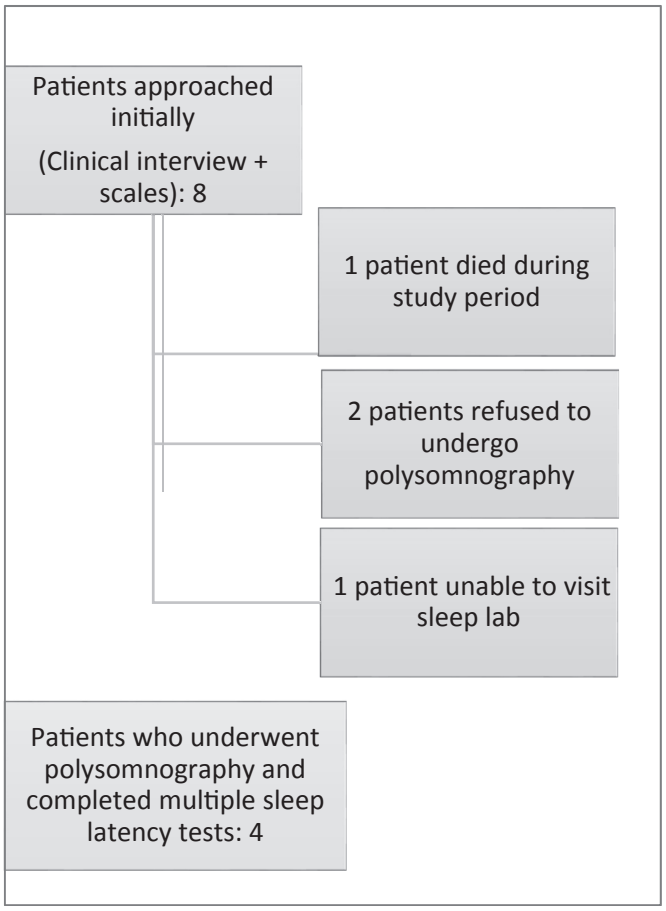

Fig. 1. Flow Chart of patients in the study.

2.5. Ethical aspects

The local ethics committee approved this study under registry number 1.855.077. All participants provided written informed consent prior to enrolment in the study.

3. Results

3.1. Clinical features

The clinical evaluation of patients is summarized in Table 1. Regarding the NPC forms, three patients had juvenile onset, three adult onset, one perinatal and one late-infantile onset. The clinical evaluation revealed normal BMI and Mallampati scores in the majority of patients. All patients had cerebellar ataxia, vertical gaze palsy, and cognitive decline. Scores ranged from 13.5 to 40 on the SARA and from 8 to 23 on the disability scale. The neurological examination also disclosed dystonia and postural tremor as common neurological signs.

3.2. Sleep evaluation

3.2.1. Subjective evaluation

Table 2 discloses sleep characteristics of eight patients with NPC in a face-to-face interview with patients and caregivers. Five patients had chronic insomnia. All of them were on psychotropic drugs and no medications were changed. All these patients reported intermediate insomnia, but initial and terminal insomnia were also described. All of the patients had an intermediate or

Table 1
Global and clinical features of eight patients with Niemann-Pick disease type C.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Sex	F	F	F	M	F	F	F	F
Age (years)	26	15	33	40	26	33	26	15
Age of disease onset (years)	6	8	10	32	16	12	20	<1 (1 month)
Consanguinity	Y	Y	N	N	N	Y	Y	N
First symptom	Cognition	Ataxia	Cognition	Gaze palsy	Psychosis	Ataxia	Sleepwalking	Hepatic
SARA	NA	13.5	25.5	16.5	20.5	24	13.5	40
Disability scale	21	8	14	10	12	12	9	23
Time in use of Miglustat (years)	0.7	1	10	5	8	2	<1	10[a]
Clinical features:								
Psychosis	N	Y	Y	N	Y	Y	Y	N
Urinary/sexual symptoms	Y	N	N	Y	N	Y	N	Y
Pneumopathy	Y	N	Y	N	N	N	N	Y
Hepatosplenomegaly[b]	N	N	Y	Y	Y	Y	Y	Y
Dystonia	Y	Y	Y	N	Y	Y	N	Y
Postural tremor	N	N	N	Y	Y	N	N	N
Seizures	Y	N	N	Y	N	N	N	Y
Vertical gaze palsy	Y	Y	Y	Y	Y	Y	Y	Y
MMSE	NA	23	12	19	14	17	21	NA
Clinical exam scale								
BMI	<17	17.3	17.6	26	18.4	23.2	23.1	NA
Mallampati scale	NA	0	1	1	4	0	1	4
Neck measurement (cm)	NA	27	–	–	–	33	–	–

NPC – Niemann Pick type C; SARA – Scale for the assessment and rating of ataxia; M– Male; F – Female; NA – not applicable; Y – Yes; N- No; MMSE – Mini-mental state examination; BMI – Body mass index.
[a] Irregular use of treatment.
[b] Ultrasound was performed after NPC diagnosis, except for patient 8, who did with 2–3 months of age.

morningness circadian pattern, measured by MEQ. Four patients had a PSQI indicating poor quality sleep, but two patients did not complete the PSQI or other questionnaires due to disease severity or death. One patient started NPC symptoms with sleepwalking and hypersomnia. The symptoms were very irregular in frequency, spending months without episodes and months with three or more episodes of sleepwalking. The diagnosis of epilepsy was excluded. Four patients exhibited clinical signs of OSA, but only one underwent PSG (Table 2). One patient had high scores on the IRLSRS indicating severe symptoms of RLS while one patient had mild RLS symptoms. Another patient had also RLS symptoms, but neurological examination disclosed restlessness in the absence of discomfort and with no marked diurnal variation, with the current diagnosis of akathisia. Two patients had high scores on the RBDSQ-BR and one had scored four points on the scale, but she had sleepwalking which is a known RBD differential diagnosis (Fig. 2).

3.2.2. *Objective evaluation*

All patients submitted to PSG had reduced and/or disorganized sleep, with lower-than-expected sleep efficiency, total sleep time

Table 2
Sleep subjective characteristics of eight patients with Niemann-Pick disease type C.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Roommate at interview	Y	Y	Y	Y*	Y	Y	Y	Y**
Subjective sleep latency (minutes)	>120	30–60	0	0	0	60	120	>120
Subjective sleep efficiency (%)	8%	85%	90%	100%	54%	71%	67%	25%
Psychotropic drugs (dose)	Trazodone 100 mg/day	N	Quetiapine 800 mg/day + periciazine 100 mg/day	N	Olanzapine 10 mg/day	Quetiapine 100 mg/day	Quetiapine 50 mg/day	Phenobarbital 100 mg/day
Number of awakenings	>3	0	3	2	>3	2	2	>3
Reason for awakenings	Unknown	Unknown	Cough	Urinary	Unknown	Urinary	Urinary	Unknown
Sleep return latency (minutes)	>30	<30	>30	<30	30	>30	<30	Unknown
Restorative sleep	Unknown	Y	Y	Y	Y	Y	N	Unknown
Cataplexy	N	N	N	N	N	N	N	Y
Snoring	>3x/week	N	2x/week	N	>3x/week	2x/week	N	NA***
Witnessed apnea	Y	N	N	N	Y	N	N	N
Mouth breathing	Y	N	N	N	Y	N	Y	Y
Unpleasant leg feeling/move urgency, during nighttime	Y****	N	N	N	Y	N	Y	N
Active during sleep	N	N	N	Final 1/3	First 1/3	N	Mid 1/3	N
IRLSRS	NA	NA	NA	NA	21	NA	4	NA
PSQI	NA	2	7	11	2	10	9	NA
MEQ	58	62	55	NA	59	51	53	63
Epworth scale	NA	3	9	8	9	3	10	NA

NA – not applicable; * his mother share the room only on trips; **three times a week with roommate; *** use of CPAP since eight years old; **** akathisia; IRLSRS – International Restless Legs Syndrome study group Rating Scale; RBDSQ-BR – Brazilian Portuguese version of REM sleep behavior disorder screening questionnaire; PSQI – Pittsburgh Sleep Quality Index; MEQ – morningness-eveningness questionnaire.

and amount of REM sleep relative to normal individuals of the same age and gender. One patient had a higher than normal arousal index and other one had excessive fragmentary myoclonus. Two patients had reduced REM sleep latency. Another three individuals had a high amount of N3 sleep. About the disorganization of sleep on EEG, there was presence of alphadelta pattern in three patient, disorganization of background electroencephalographic activity in two patients, and presence of sigma activity on REM sleep in one patient. One patient had REM without atonia, displaying symptoms prior to starting on sertraline, which was not discontinued before PSG (Table 3). RDI revealed one moderate OSA and two mild OSA cases, and this two had no clinical complaints and had these respiratory events only at dorsal position. The MSLT proved abnormal in only one patient, with low mean sleep latency and presence of five SOREMs. Another patient reported cataplexy but did not undergo the PSG or perform the MSLT.

3.3. Sleep disorder management

After sleep evaluation, we performed treatment/management approaches to the sleep disturbances. Patients 2 and 7 were advised for not sleeping on dorsal position to avoid apnea and/or hypopnea. Patients 3 and 6 had medications adjusted and sleep hygiene implemented with good therapeutic response. Patient 3 is now using quetiapine 700 mg/day, ziprasidone 120 mg/day, clozapine 25 mg/day, and citalopram 20 mg/day. Patient 6 is using clozapine 100 mg/day, zolpidem 10 mg/day, and venlafaxine 150 mg/day. Patient 7 started methylphenidate 10 mg/day and were advised for naps for narcolepsy management with great response. For psychotic control, we switched quetiapine 25 mg to risperidone 1 mg/day. Patient 5 is awaiting for continuous positive airway pressure device and ferritin levels.

4. Discussion

This study demonstrated that other sleep disorders, besides cataplexy, were found in the NPC population assessed. Chronic insomnia, OSA, probable and confirmed RBD and RLS were detected in the patient sample. These results suggest that the widespread involvement of areas of the central nervous system in NPC patients, including the thalamus, cerebellum, brainstem and diencephalon, reported in previous studies could also affect areas that regulate the sleep-wake cycle [16]. The present results are in agreement with those of a mouse model of NPC showing decreased tyrosine-hydroxylase immunoreactivity in the locus ceruleous and preserved choline acetyltransferase immunostained neurons in the pedunculopontine tegmental nucleus of NPC1 mice [17].

A wide range of neurological symptoms have been described in NPC patients [1]. Cerebellar ataxia, vertical gaze palsy and cognitive decline were identified in all patients of the present study. These findings are consistent with previous studies showing that the main NPC psychiatric and neurological symptoms are dementia, cognitive pre-senile decline, vertical gaze palsy and gelastic cataplexy [3].

To the best of our knowledge, there are no previous reports of sleepwalking symptoms as a first clinical finding or during the course of NPC. This finding in our patient may have been mere coincidence, as sleepwalking is common in early age, but may have been caused by involvement of subcortical structures in NPC and/or by fragmented sleep observed in this specific case.

Chronic insomnia was found in five patients, all of whom had exhibited NPC symptoms for more than 10 years. In agreement with our study, Nevsimalova et al., also described a patient with insomnia at a later stage of the disease [18]. We hypothesized that, in NPC disease, there is a gradual and progressive involvement of structures related to the sleep-wake cycle in the brainstem and diencephalon. In addition, as NPC progresses, neuronal death becomes overt, predominantly affecting certain regions, particularly Purkinje cells of the cerebellum. Indeed, the involvement of the cerebellum may play a role in sleep control. The output neurons of the cerebellum are connected with the sleep-wake network. As a result, patients with ataxia could present a variety of sleep disorders [19]. Moreover, motor dysfunction caused by the disease, restricting patients to bed, together with the emergence of psychiatric symptoms such as psychosis, could be other causative factors of insomnia complaints.

To our knowledge, there are no previous studies reporting OSA in NPC patients. NPC patients have impaired coordination of respiratory muscles during sleep and decreased respiratory muscle tonus. Notably, our patients were using medication that could have interfered with this muscle tonus. It is also important to mention that obesity was not an important risk factor in this group of patients. Of further note, the three patients with PSG-confirmed OSA had psychosis. Although the relationship between OSA and psychosis is unclear, a previous study of 1825 psychotic patients with a mean age of 38.4 years showed that 41.9% reported having symptoms associated with OSA (snoring and breathing pauses during sleep) in the past year on the University of Maryland Medical Centre Questionnaire, where almost 80% had no fixed roommate.

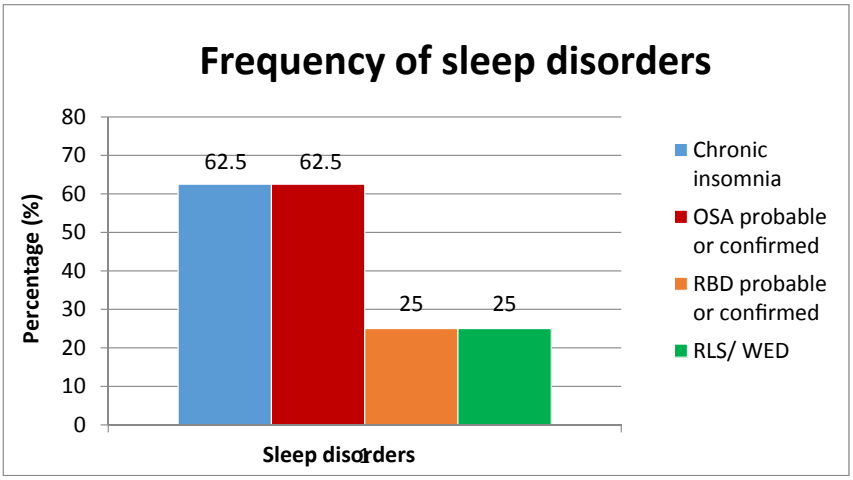

Fig. 2. Frequency of major sleep disorders in patients with Niemann-Pick disease type C according to the Third International Classification of Sleep Disorders (n = 8). (RBD, REM sleep behavior disorder; OSA, Obstructive Sleep Apnea; RLS/WED, Restless Legs Syndrome/Willis-Ekbom Disease).

Table 3
Polysomnography and MSLT measures of four NPC patients.

	NPC patients				Normal reference values[a]
	Patient 2	Patient 5	Patient 6	Patient 7	
PSG parameters					
Total sleep time (h)	4.8	3.9	6.4	5.5	7.5–8
Sleep efficiency (%)	34.5	17.7	43.6	65.2	80–85
WASO (min)	67	203	44	54.5	15–110
Sleep latencies (min)					
Sleep onset	39.7	13.4	15.8	53.7	<30
REM	211	81	30	22.5	90–120
SWS	93.2	26.9	86.8	118.2	
Sleep stages (%)					
NREM1	8.2	19.4	13.8	5.1	5
NREM2	52.9	46.9	47.0	43.4	50
NREM3	35.1	31.1	21.3	26.7	20
REM	2.5	1.3	15.3	16.8	25
EFM	–	–	–	+	–
Total arousal index	23.71	11.47	13.57	9.68	6–22
RDI total	11.96	18.93	2.49	7.14	<5
PLMI total	0	0	2.34	6.33	<15
Atonia in REM sleep	Y	Y	Y	N	Y
MSLT parameters					
Mean latency (min)	19.9	12	15.9	2.5	10–15
SOREMs	0	0	0	5	0

WASO – wake after sleep onset; PSG – polysomnography; REM – rapid eye movement; SWS – slow wave sleep; PLM – periodic limb movement; MLST – multiple sleep latency test; RDI – Respiratory Disturbance Index; EFM – excessive fragmentary myoclonus.
[a] Normal population with same sex and age.

This finding could be a coincidence, but since the prevalence of OSA in the general Brazilian population is 32.8%, the result might be explained by this previously reported relationship between psychosis and OSA [20,21].

Three patients had clinical features of RLS, one of whom had akathisia, a known differential diagnosis. No previous reports of an association between NPC with RLS were found. Nevsimalova et al., performed a retrospective study of 22 NPC patients. The authors reported restless sleep in 27.2% of the sample but failed to describe symptoms or exclude RLS mimics [18]. The association of RLS with a variety of diseases and disorders reflects the multifactorial etiology of this syndrome. The current knowledge points to iron deficiency and chronic inflammation as two major causes of the related dopaminergic dysfunction. However, the pathophysiology is more complex than previously thought, with involvement of thalamocortical circuits, which are probably affected in NPC patients [22].

One patient in the present study had excessive sleepiness. The same patient had polysomnographic and MSLT findings of narcolepsy, but the total sleep time during PSG was insufficient. Furthermore, the medications were not stopped before the MSLT [23,24]. The production of hypocretin in the lateral hypothalamus may be affected in NPC [2,18].

Cataplexy was diagnosed in only one patient that had an early-infantile form of the disease. Unfortunately, this patient was not able to perform PSG due to the severity of disease nor the orexin dosage. This symptom is commonly described in late-infantile and juvenile forms of NPC [4,18]. NPC is associated with increased cholinergic activity and decreased monoaminergic activity in the upper pontine tegmentum, essential in the transition from non-REM to REM sleep [25].

Two patients reported nightmares and dream enactment at the end of sleep period. Moreover, the behaviors during sleep have already injured the bed partners. REM sleep behavior disorder (RBD) is characterized by loss of skeletal muscle atonia during REM sleep and is associated with nightmares and dream enactment. There is an association of RBD with diseases promoted by the deposition of alpha-synuclein in neurons, as well as with narcolepsy, which could explain the symptoms of patient 7. Within the brainstem, there are neuronal nuclei responsible for musculoskeletal atony during REM sleep (sublaterodorsal nucleus and magnocellular reticular formation) and the involvement of these nuclei in NPC physiopathology could offer another explanation for this comorbidity [26]. Another explanation would be the involvement of orexinergic cells, as suggested before [18].

Our study also revealed disorganized sleep in all four patients, with lower-than-expected sleep efficiency, total sleep time and total amount of REM sleep lower relative to normal individuals of the same age and gender. Vankova et al., reported similar findings to the results of our study. However, the same authors reported excessive fragmentary myoclonus in all of their patients, a phenomenon seen in only one patient from the present sample. As for EEG elements, Vankova et al., showed similar alterations on sigma activity atypical forms of sleep graphoelements and presence of alphadelta, showing a poor quality of sleep [2]. Furthermore, the authors described MSLT abnormalities in three out of five patients, while only one of our patients showed alterations in these parameters, such as mean sleep latency and SOREMs [2]. The present study had some limitations: only half of the patients underwent PSG and performed MSLT, the small sample, the absence of a control group, the impossibility to discontinue medications before PSG and the MSLT and the lack of orexin levels.

5. Conclusion

Our study suggest that sleep disorders are highly prevalent in NPC patients, with disorganization of sleep character (increasing with NPC duration), taking surely a substantial share in their quality of life.

Future controlled studies involving a larger number of patients and sleep-related interventions in NPC patients are warranted. Based on our results, careful clinical evaluation of sleep-related aspects in NPC patients should be part of routine practice, since these alterations could cause a significant reduction in their quality of life, cognition and morbimortality.

Authors' roles

DMR, MASN, and CRM were involved in study conception and design, acquisition of raw data, analysis, and interpretation of data, and drafting of the article.

PBN was involved in study conception and design, analysis, and interpretation of data, drafting of the article and critical review of the manuscript.

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We have nothing to disclose.

Ethical statement

Patients signed an informed consent form and allowed publication of this data.

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Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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.2019.02.007.

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