Research Article

Narcolepsy and Idiopathic Daytime Hypersomnia: A Study of Cohort in the Chilean Population

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Abstract

Introduction: Central disorders with hypersomnolence (CDH) are a group of sleep disorders characterized by excessive daytime sleepiness (EDS) that can be related to REM-sleep dissociative symptoms. They have a low prevalence in the population and may not be explained by other medical conditions.

Materials and methods: A cohort of 59 Chilean patients with the most common types of CDH were studied. Clinical data, and results of polysomnography (PSG) plus multiple sleep latency tests (MSLT) were analyzed..

Results: The median age of the cohort was 35.26 ± 13.23 years (69.5% female). Diagnosis of narcolepsy Type 1, narcolepsy Type 2, and idiopathic daytime hypersomnia, were determined in 54.2%, 23.7% and 22% of patients respectively. All patients reported EDS, while 57.6%, 81.4% and 78% reported cataplexy, sleep paralysis and hypnagogic/hypnopompic hallucinations respectively. Polysomnographic studies showed non relevant alterations in the majority of patients. The MLTS was abnormal in all patients, 78% of them with 2 or more sleep onset REM periods (SOREMP). In 52.5% of cases, the delay in final diagnosis was more than 5 years. About a third of patients had another sleep disorder that could not explain the severity of EDS. We observed a comorbidity with an immunological disorder in 30.5% of patients.

Conclusion: The EDS is the main symptom in CDH. Related REM-sleep symptoms and MSLT alterations were the second most important features to establish final diagnosis.   However, we observed a significant delay in CDH diagnosis in the majority of patients.

Keywords: Narcolepsy, Cataplexy, Hypersomnia, Excessive daytime sleepiness.

Introduction

Central hypersomnolence disorders (CHD) are a group of sleep disorders that primarily involve excessive daytime sleepiness (EDS) not attributable to another cause. The International Classification of Sleep Disorders (ICSD-3) includes narcolepsy type 1 and type 2 (NT1 and NT2), idiopathic hypersomnia (IH), and Kleine-Levine syndrome (KLS) (1, 2). The prevalence of CHD varies between 4 and 160 cases/100,000 inhabitants, depending on the series (5,6,7,8,9). The prevalence in Chile is unknown.

EDS is the inability to maintain wakefulness during the day, with decreased alertness and irresistible tendency to sleep. It can be measured subjectively with the Epworth Sleepiness Scale (ESE) (3) and objectively through the multiple sleep latencies test (MSLT) (4).

Narcolepsy is a chronic and rare sleep disorder characterized by rapid and inappropriate transitions between waking and sleeping states. Semiologically it is characterized by EDS as the cardinal axis, associated with manifestations of REM sleep dissociation (cataplexy, hypnagogic or hypnopompic hallucinations, sleep paralysis) and fragmentation of nocturnal sleep. The disease has two peaks of incidence, the highest at around 15 years of age and another at 35 years of age, but it can occur at any age (10). The diagnosis is clinical and is supported by an altered MSLT (at least 2 naps with REM stage and decreased average latency at sleep onset). PSG may show a decreased latency to the first REM stage (less than 15 minutes from sleep onset). IH is also characterized by a very significant EDS, but patients do not report symptoms of REM sleep dissociation.

CHD is usually underdiagnosed, presenting a latency of several years between the onset of symptoms and definitive diagnosis (33). This leads to delayed treatment, poor quality of life, and a negative economic impact on patients (34), given that most are of productive age.

In the following work we present the epidemiological and clinical characteristics of a group of Chilean patients diagnosed with one of the most common forms of CHD. The results are compared with those existing in the international literature.

Materials and Methods

A cohort study of patients with diagnoses of narcolepsy and IH was performed. The included patients signed an informed consent. This study conformed to the protocols of the Declaration of Helsinki and was approved by the ethics committee of the Servicio de Salud Metropolitano Oriente (SQL 7976).

Recruitment of patients: Between January and June 2021, neurologists specializing in sleep disorders in the city of Santiago were contacted and asked to invite patients under control for some type of CHD to participate in the study. A total of 92 patients were referred, of which 28 did not complete all the evaluations and 5 were excluded because they did not have tests certifying the diagnosis. Finally, 59 patients were included in this study.

Each patient underwent a clinical interview, was administered the Pittsburgh Sleep Quality Index (PSQI) and the results of their PSG and TLMS were recorded. Subsequently, a descriptive statistical analysis of the variables found was performed.

Results

The mean age of the patients was 35.26±13.23 years (Table1, Figure1), 69.5% were female. 89.8% of the patients were adults between 18 and 60 years old. 45.8% of the patients had a body mass index (BMI) in the normal range, while 37.3% and 13.6% had a BMI in the overweight and obese range, respectively.

The age of symptom onset ranged from 10 to 55 years. In 42.4% the symptoms appeared before the age of 18 years, while only 1.69% started between the ages of 32 and 37 years.

All patients consulted for presenting EDS with elevated baseline ESE score (> 10 points). Regarding REM sleep dissociation symptomatology, cataplexy (57.6%), hypnagogic or hypnopompic hallucinations (78%), and sleep paralysis (81.4%) stood out. 84.7% presented poor sleep quality with 5 or more points on the PSQI despite being in treatment.

In all patients, the diagnosis was confirmed with MSLT of 5 naps. The 79.7% presented a severely decreased average latency (less than 5 minutes), while 20.3% presented latencies between 5 and 8 minutes. Seventy-eight percent of the group presented REM stage in at least two of the five naps.

In most cases the PSG did not show specific alterations. The mean AHI was 2.81 ± 2.09 events/hour. Only 3 patients had an index greater than 5 and the maximum value was 11 events/hour. None of the cases referred a shortened latency to the first REM stage.

In 33.89% of the cases, patients were referred with a diagnosis of another sleep disorder: 10 patients (16.9%) had a clinical diagnosis of restless legs syndrome; while 8 patients (13.6%) had a diagnosis of rhoncopathy or mild OSA in addition to CHD.

Finally, the diagnosis of NT1 was made in 54.2%, while the diagnosis of NT2 was determined in 23.7% and that of HI in 22% of patients.

A significant delay in definitive diagnosis was observed in most patients. In 35.6% of the cases the diagnosis was established between 5 and 10 years after the onset of symptoms. In 10 patients (16.9%), the diagnosis took more than 10 years to be established.

Table 1. Summary of Quantitative Variables.

	Age	BMI	Age of onset of symptoms	Years of diagnosis of Narcolepsy	Average Latency MLST (minutes)	N° naps with REM	Pittsburgh
Minimum	10	17,2	1	0	0,83	0	3
Median	32	25,2	18	5	3,75	2	8
Maximum	81	47,5	55	33	7,5	4	26
Range	71	30,3	54	33	6,67	4	23
Average	35,44	26,44	19,88	6,644	3,725	2,051	9,407
SD	13,28	5,86	10,34	7,203	1,636	0,8595	4,843

Descriptive statistical analyses of the quantitative variables in the study are shown. From the data in Table 1, we get the box charts of the variables, in Figure 1.
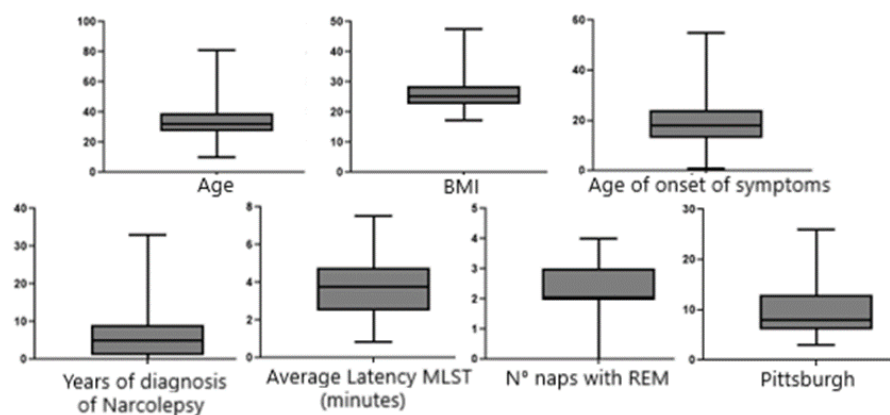

Figure 1. *Graphics the box charts of the variables.*

Among the comorbidities referred (Table 2 and 3), 30.5% of the group had an autoimmune disease, the most frequent being Hashimoto's thyroiditis in 8/59 patients (13.6%). No patient was referred with diagnoses of other endocrine disorders or dysautonomia.

Regarding pharmacological therapy, 6.8% received only one type of drug, 20.4% received 2 different drugs and 71.2% were on 3 or more drugs for this condition. The most commonly used drugs were SSRI antidepressants in 66.1%, amphetamine derivatives in 54.2%, wakefulness promoters such as Modafinil or Armodafinil in 52.5%. One patient was using sodium oxybate and Pitolisant at the beginning of the study, the first of these drugs was the only one that managed to control hypersomnolence and severe cataplexy.

Table 2: List of immunological co-morbidities.

Co-morbidities	Frequency (Number of patients)	Percentage	Cumulative Percentage
Psoriatic Arthritis	1	1,7	1,7
Ulcerative colitis	1	1,7	3,4
Celiac disease	2	3,4	6,8
Celiac disease, Allergic, Psoriatic	1	1,7	8,5
Autoimmune gastritis – Rush	1	1,7	10,2
Hashimoto disease	8	13,6	23,7
Gluten intolerance	1	1,7	25,4
SLE	1	1,7	27,1
Without comorbidities	41	69,5	96,6
Psoriatic	1	1,7	98,3
Rosacea, rheumatoid arthritis	1	1,7	100,0
Total	**59**	**100,0**	

Several immunological disorders are observed in this table, the most frequent ones were hypothyroidism in 8 patients, celiac disease in 3 patients, and psoriatic disease in 3 patients. On the other hand, some patients present more than one immunological disease. (SLE: Systemic lupus erythematosus)

Table 3: List of other associated sleep disorders.

Another sleep diagnosis	Frequency	Percentage	Cumulative Percentage
Confusional Arousal	1	1,7	1,7
PLMS	1	1,7	3,4
Non	39	66,1	69,5
Nightmare	1	1,7	71,2
Slight Snoring	3	5,1	76,3
Slight OSA	2	3,4	79,7
Slight OSA and Snoring	1	1,7	81,4
RLS and Snoring	2	3,4	84,7
Somniloquy	1	1,7	86,4
RLS	6	10,2	96,6
RLS - PLMS	1	1,7	98,3
RLS and SRED	1	1,7	100,0
Total	**59**	**100,0**	

Sleep disorders that were found associated in these patients were analyzed and treated in a particular way in the cases that were required and, they did not modify the initial symptoms described by the patients, ruling out as the causes of the CHS or the REM sleep dissociation symptoms. The most frequent reason was RLS in 10 patients, which were found isolated in 6 patients, and the remaining ones were associated with another sleep disorder.

(PLMS: periodic limb movements during sleep; Non: Without sleep disease; OSA: Obstructive sleep apnea; RLS: Restless Leg Syndrome; SRED: Sleep-Related eating Disorder)

Discussion

A Chilean study of 59 patients diagnosed with CHD is presented, of which the most frequent cause found was NT1 (54.2%). All patients presented with EDS and with an altered MSLT. The vast majority of patients (84.7%) reported poor sleep quality as measured by the PSQI.

EDS remains the cardinal symptom for the diagnosis of CHD. However, it is poorly evaluated in clinical practice and is often confused with fatigue or depression. A study in a Chilean population established a cut-off point of 11 points in EDS for the diagnosis of sleep apnea (3), but the recommendation of the American Academy of Sleep Medicine (AASM), with a cut-off point of 10 points to define EDS, continues to be the most widely used (11,12).

The MSLT objectifies EDS by determining an average sleep onset latency of less than 8 minutes, this value was established by expert consensus (13). The MSLT is a very sensitive test measuring the effects of sleep deprivation, but it is less sensitive for diagnosing other entities that present with EDS, since it can show inconsistent or contradictory results, even alterations can be observed in healthy subjects (14, 15). Because of this, MSLT should be performed after a PSG that rules out some of these confounding variables (16). Studies in patients with narcolepsy have shown that most of them have an average latency of less than 5 minutes (15), suggesting a higher diagnostic sensitivity of MSLT for narcolepsy. In our cohort of patients, 100% had MSLT with time less than 8 minutes and 80% had latencies less than 5 minutes.

Cataplexy, defined as the sudden loss of muscle tone during wakefulness, triggered by emotions and explained by REM sleep interference, is the only symptom that differentiates the two types of narcolepsies and was present in 57.6% of our patients. The intensity of cataplexy is variable, and its severity has an inverse relationship with cerebrospinal fluid hypocretin levels. A concentration ≤ 110 pg/mL is considered one of the supportive tests for the diagnosis of narcolepsy (1). In Chile, the lack of access to measure this peptide forces the diagnostic confirmation to be made through a MSLT and a PSG. The presence of REM stage in at least two of the five naps of the MSLT, or a nap with REM stage plus a decreased latency to REM sleep in the PSG allows making the definitive diagnosis of narcolepsy (1).

The other symptoms present in both types of narcolepsies translate REM stage dissociation. Sleep paralysis, hypnagogic and hypnopompic hallucinations were present in a high percentage of our group. In our cohort we observed a lower percentage of patients with NT1 versus the number presenting cataplexy (54.2% vs 57.6%), this could be explained by the fact that patients with compatible clinical features, but negative electrophysiological studies should be classified as HI according to AASM criteria.

IH presents with EDS, without symptoms of REM sleep dissociation. Furthermore, unlike narcolepsy, patients with IDD do not have restorative naps and sleep inertia is a frequent symptom that differentiates them from other forms of HCT (1). For many authors, this group of patients are virtually indistinguishable from those with NT2, and in the absence of a biological marker the differential diagnosis is complex (17). It has been proposed that HI and NT2 without hypocretin deficit could be merged as "narcolepsy spectrum disorder" and patients suffering from NT2 with altered hypocretin levels could be merged with NT1 (18). Other CSF studies in patients with HI and prolonged total sleep time have shown alterations in GABA-A receptor activity levels (17).

The high prevalence of autoimmune diseases, which do not explain the symptoms of CHD, stands out in our study population. The percentage of our patients with Hashimoto's thyroiditis is almost double that described in the general population (35). Current studies suggest that narcolepsy may be a disease of autoimmune origin, affecting a genetically susceptible population. The association of the major histocompatibility complex (HLA) genotype with narcolepsy has been known since 1983. Individuals with DRB1*1501 and DQB1*0602 alleles show a greater genetic predisposition to present the disease. The DQB1*0602 allele is found in 95-98% of Caucasoid patients with narcolepsy and is a good marker of disease and is associated with onset and severity of cataplexy (19,20). Hypocretin-specific autoreactive TCD8+ cells have been detected in blood and CSF of several patients with narcolepsy, supporting the autoimmune origin of the disease (21). However, the detection of antibodies against Hypocretin-1 or its receptors shows no association with HLA types, presence of cataplexy, or nighttime sleep disruption (22). A study of narcolepsy patients with HLA DQB1*0602, shows temporal variations in CSF Hypocretin-1 and histamine levels, suggesting the possibility of monitoring these markers over time to indicate immunological therapies in early stages of the disease (23).

Another aspect that reinforces the autoimmune hypothesis in the genesis of narcolepsy is its association, especially NT2, with other comorbid immune-mediated diseases, such as multiple sclerosis, systemic lupus erythematosus, psoriasis, inflammatory bowel disease, among others (24). In addition, a relationship has been found between the severity of cataplexy in NT1 with allergic disorders and the presence of immune-mediated disease (24,25).

In our group, 33.9% showed a different sleep disorder associated with CHD. Other series report that, in patients with narcolepsy, 55% present with sleep-related movement disorders, 34% with parasomnias, 24% with sleep breathing disorders and 28% with insomnia. REM sleep without atonia and periodic limb movements are present in the majority of patients (90% and 75%, respectively) (26, 27). In our study group, we observed that restless legs syndrome was the most frequently associated sleep disorder. Snoring and mild obstructive sleep apnea syndrome were present in 16.9% of cases.

The treatment of CHD is symptomatic. There are no disease course-modifying drugs. Of our patients, 71.4% were treated with three or more drugs, mostly wakefulness promoters and antidepressants. Sodium oxybate is considered the first-line drug for the treatment of narcolepsy; it decreases EDS, cataplexy seizures and sleep fragmentation. This drug is not available in our environment, which makes it necessary to use other alternatives. Modafinil is the first line drug for the management of EDS, its mechanism of action is not completely known; it is attributed to a reinforcement of presynaptic transmission of dopaminergic and noradrenergic neurons. The use of tricyclics is in second-line treatment of cataplexy. Benzodiazepines can be used to decrease sleep fragmentation (28). Pitolisant, a histamine presynaptic H3 autoreceptor blocker, has been approved for the treatment of EDS in NT1 (29) and was used by a patient in our group, imported from Spain, with modest results. Antidepressants are useful in narcolepsy for the management of cataplexy, the most widely used being venlafaxine. Its clinical effect would be mediated by a decrease in sleep fragmentation and inhibition of REM expression.

Conclusion

The clinical characteristics of the cohort presented in this study suggest a guideline for the diagnosis of the different forms of CHD in our setting. This would help to reduce the delay in the initiation of treatment of disorders that have a significant impact on the quality of life and negative socioeconomic impact on patients (30,31, 32).

Our work has the strength of being able to describe a local cohort of patients with CHD, whose diagnosis is based mainly on the referred symptoms. Twenty-eight patients (47.6%) had the complete clinical tetrad for the diagnosis of narcolepsy (EDS, cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis).

A weakness of the present study is the small number of cases described, due to the low prevalence and diagnostic delay inherent to these disorders. In addition, there is the bias of corresponding to a very selected group of patients, whose diagnoses have already been established by highly specialized physicians.

The main diagnostic key is to recognize EDS, for which we recommend as clinical definition a score on the Epworth scale greater than 10 points. Then rule out the presence of any morbid condition that could explain the symptom (another sleep disorder, effects of a drug, chronic sleep deprivation, among others). In case of clinical suspicion, it is suggested to perform a PSG followed by a MSLT to detect EDS with an average latency of less than 8 minutes. The presence of REM sleep dissociation symptoms leads to a diagnosis of narcolepsy, which is confirmed if the MSLT shows at least two naps with REM stage, or a nap with REM stage plus a decreased latency to REM stage in the PSG.

The diagnosis of HI is one of exclusion and is based on the existence of EDS of primary cause, without symptoms of REM stage dissociation, with significant sleep inertia. The diagnosis is confirmed with a MSLT with low average latency at sleep onset, but less than two naps with REM stage, plus a normal PSG.

Author Disclosure Statement

Acknowledgments

Abbreviations

CHD: Central hypersomnolence disorders; EDS: Excessive daytime sleepiness; ICSD-3: International Classification of Sleep Disorders; NT1: Narcolepsy Type 1; NT2: Narcolepsy Type 2; KLS: Kleine-Levine syndrome; IH: Idiopathic daytime hypersomnia; ESE: Epworth Sleepiness Scale; MSLT: Multiple Sleep Latency Test; PSG: Polysomnography; BMI: Body Mass Index, PSQI: Pittsburg Sleep Quality Index. AHI: apnea-Hypopnea Index. OSA: Obstructive Sleep Apnea; AASM: American Academy of Sleep Medicine; CSF: Cerebrospinal Fluid. SOREMP: Sleep onset REM periods

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