Brazilian guidelines for the diagnosis of narcolepsy

Diretrizes brasileiras para o diagnóstico da narcolepsia

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Abstract

This manuscript contains the conclusion of the consensus meeting on the diagnosis of narcolepsy based on the review of Medline publications between 1980-2010. Narcolepsy is a chronic disorder with age at onset between the first and second decade of life. Essential narcolepsy symptoms are cataplexy and excessive sleepiness. Cataplexy is defined as sudden, recurrent and reversible attacks of muscle weakness triggered by emotions. Accessory narcolepsy symptoms are hypnagogic hallucinations, sleep paralysis and nocturnal fragmented sleep. The clinical diagnosis according to the International Classification of Sleep Disorders is the presence of excessive sleepiness and cataplexy. A full in-lab polysomnography followed by a multiple sleep latency test is recommended for the confirmation of the diagnosis and co-morbidities. The presence of two sleep-onset REM period naps in the multiple sleep latency test is diagnostic for cataplexy-free narcolepsy. A positive HLA-DQB1*0602 with lower than 110pg/mL level of hypocretin-1 in the cerebrospinal fluid is required for the final diagnosis of cataplexy- and sleep-onset REM period -free narcolepsy.

Descriptors: Cataplexy; Narcolepsy; Diagnosis; Disorders of excessive somnolence; Polysomnography

Resumo

*Este artigo relata as conclusões da reunião de consenso com médicos especialistas sobre diagnóstico de narcolepsia baseada na revisão dos artigos sobre narcolepsia listados no Medline entre 1980 e 2010. A narcolepsia é uma doença crônica de início entre a primeira e segunda décadas de vida do indivíduo. Os sintomas essenciais são cataplexia e sonolência excessiva. A cataplexia é definida como episódios súbitos, recorrentes e reversíveis de fraqueza da musculatura esquelética desencadeados por situações de conteúdo emocional. Os sintomas acessórios são alucinações hipnagógicas, paralisia do sono e sono fragmentado. Critérios de diagnóstico clínico de acordo com a Classificação Internacional dos Transtornos do Sono são de sonolência excessiva e cataplexia. Recomenda-se a realização de polissonografia seguida do teste de latência múltipla do sono em um laboratório de sono para confirmação e diagnóstico de comorbidades. Quando não houver cataplexia, deve haver duas ou mais sonecas com sono REM no teste de latência múltipla do sono. Tipagem HLA-DQB1*0602 positiva com níveis de hipocretina-1 abaixo de 110pg/mL devem estar presentes para o diagnóstico de narcolepsia sem cataplexia e sem sonecas com sono REM.*

Descritores: *Cataplexia; Narcolepsia; Diagnóstico; Sonolência excessiva; Polissonografia; Transtorno do sono*

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Introduction

Narcolepsy is a chronic neurodegenerative and likely autoimmune disorder characterized by excessive daytime sleepiness and dissociative manifestations of REM sleep such as cataplexy, sleep paralysis, hypnagogic hallucinations and sleep onset REM periods (SOREMP).[1] The clinical importance of narcolepsy is disproportionate to its prevalence rate because the disorder has severe psycho-social and functional impacts. The pathogenesis of narcolepsy in humans involves environmental factors and a specific autoimmune genetic platform that together lead to hypocretin neuronal loss.

1. Epidemiology of narcolepsy

The prevalence of narcolepsy with cataplexy is 15 to 50 cases per 100,000 people (0.015% to 0.05%), and the prevalence of narcolepsy without cataplexy is 56 cases per 100,000 people (0.056%).[2-6]

The prevalence of narcolepsy with and without cataplexy is estimated at 1.37 per 100,000 people per year,[4] with a peak incidence in the second decade of life. Narcolepsy affects both males and females (1.4-1.8:1).[4]

2. Genetics of narcolepsy

Both genetic and environmental factors contribute to narcolepsy, but alone neither is sufficient or necessary to elicit narcolepsy with cataplexy.[7] The risk of narcolepsy developing in a first-degree relative of a narcoleptic individual is 10 to 40 times greater than the risk for the general population. The frequency of narcolepsy with cataplexy in first-degree relatives of narcoleptics is 2.90% to 3.20%.[7] The concordance rate of monozygotic twins for narcolepsy with cataplexy is 25% to 31%.[7]

There is a significant association of narcolepsy with the DQB1*0602 allele of the major histocompatibility complex (HLA). The prevalence rate of HLA-DQB1*0602 is 88% to 98% in the narcoleptic population with cataplexy, 40% to 60% in the narcoleptic population without cataplexy, and 12% to 34% in the general population[8-13] (Table 1). In the southeastern population of Brazil, the prevalence of HLA-DQB1*0602 is 13.6% among Caucasians[14] and 14.30% in Mulattos.[15]

Recent genome-wide association studies of HLA-DQB1*0602-positive European Caucasians, healthy Americans, and narcoleptics with cataplexy have identified the existence of a polymorphism in the T-cell receptor alpha *(TRA)* gene.[16,17] The *TRA* gene encodes a protein that activates cytotoxic CD8 cells and CD4 helper cells, resulting in susceptibility to the destruction of hypocretinergic HLA-DQB1*0602-positive cells.[16,17] These results suggest that narcolepsy is an autoimmune disease with HLA haplotype and a *TRA* polymorphism as risk factors.

Other genes are involved in the genetics of narcolepsy. For example, a polymorphism in the catechol-O-methyl-transferase (COMT) gene, which encodes the enzyme that inactivates dopamine and noradrenaline, influences the manifestation of narcoleptic symptoms and the response to treatment with modafinil, particularly in females.[18,19]

3. Symptoms

The two essential symptoms are excessive sleepiness (sensitive, but non-specific) and cataplexy (highly specific). Sleep paralysis, hypnagogic hallucinations, and fragmented nocturnal sleep are considered accessory symptoms. Thus, these five features form the classical pentad of narcolepsy symptoms:[20-24]

- daytime sleepiness;
- cataplexy;
- sleep paralysis;
- hypnagogic hallucinations; and
- fragmented nocturnal sleep.
- Other manifestations of narcolepsy are:
- episodes of automatic or stereotypic behaviors;
- nightmares;
- cognitive deficits;
- obesity;
- parasomnias;
- olfactory deficits;
- type II diabetes.

1) Excessive sleepiness (ES)

ES is the symptom in 90% to 94% of the cases and is the most important complaint made by patients. ES is chronic, daily and occurs regardless of how long the patient sleeps during the night.

The main clinical features of ES are:

- sensation of sleepiness of constant or varying intensity, lasting one or more hours;
- irresistible sleep attacks despite the attempt to remain awake;
- multiple naps throughout the day which may alleviate sleepiness for a few hours in the adult population with narcolepsy;
- the relief of sleepiness provided by naps reflects the intensity of background sleepiness and is specific for differential diagnosis; and
- fluctuations in attention and concentration levels.

2) Cataplexy

Cataplexy is characterized by sudden, recurrent, and reversible episodes of skeletal muscle weakness (excluding the diaphragm) that occur while awake. Cataplexy attacks are triggered by emotional stimuli and are dissociative phenomena of REM sleep (wakefulness along with muscular atonia).

Cataplexy is the most specific symptom and it is pathognomonic of narcolepsy with low or absent CSF hypocretin-1. Cataplexy is the most specific diagnostic marker of narcolepsy. Cataplexy

Table 1 - Prevalence rates of HLA and hypocretin-1 in the CSF

Diagnosis	HLA-DQB1*0602 positive	Hypocretin - 1 ≤ 110pg/mL
Narcolepsy with cataplexy	> 90%	85 -90% > 90% HLA positive
Narcolepsy without cataplexy	40-60%	10-20% (almost all HLA positive)
General population	12-34%	-

generally emerges simultaneously with ES, although cataplexy attacks can appear years later.

Clinical features of cataplexy attacks are:

• sudden and recurrent episodes of axial skeletal muscle atonia, limb weakness occurs bilaterally;

• the attacks are triggered by situations with strong positive emotional content (e.g., laughing) or by fear or anger;

• average duration of a few seconds up to ten minutes;

• consciousness preserved, at least at the beginning of the attack; hearing and auditory comprehension preserved during the attack;

• the attacks end suddenly with return of muscular tone without mental confusion or amnesia; and

• breathing during the attack remains normal.

3) Hallucinations

Hypnagogic and hypnopompic hallucinations (HH) are dream-like experiences occurring in the awake-sleep or sleep-awake transitions, respectively. They occur in 20% to 65% of narcoleptics and are generally visual or somato-sensorial (i.e., "out of body" sensations), but auditory, vestibular or multi-sensorial forms have also been described.[20-24]

Hallucinations can accompany or follow cataplexy and sleep paralysis attacks. Terrifying hypnagogic hallucinations occur in about 4% to 8% of narcoleptics.

4) Sleep paralysis

Sleep paralysis is the total incapacity to move that occurs when falling asleep or when in the transition from sleep into wakefulness. The patient remains temporarily incapable of accomplishing voluntary acts but awareness is maintained. Sleep paralysis can be accompanied by the sensation of inability to breathe and by varied hallucinations in up to 50% of cases. Episodes of sleep paralysis last from one to ten minutes with an average duration of two minutes and ends abruptly after mental effort or by means of external sensory stimulation.

5) Fragmented nocturnal sleep

Multiple awakenings, excessive body movements during sleep, and poor sleep quality occur in up to 90% of patients, especially in those over 35 years of age. There is no increased total sleep time in narcolepsy and no relation between fragmented nocturnal sleep and sleepiness severity.[20-24]

6) Other manifestations of narcolepsy include[20-24]:

a) Episodes of automatic behaviors and 8% to 40% of cases (automatic behaviors with amnesia may occur, ranging from repetitive movements to driving a vehicle without awareness of doing it);

b) Cognitive symptoms (narcoleptic individuals present attention deficits that become apparent when performing long, monotonous, and repetitive psychomotor tasks that are dependent on the level of alertness).

4. Ethiopathogenesis of narcolepsy

1) Dysfunction of the hypothalamic hypocretin system

The hypocretinergic system is located in the posterolateral perifornical region of the hypothalamus.[25] Type 1 and type 2 hypocretins are excitatory neurotransmitter peptides produced exclusively by these hypothalamic cells. The hypocretin system has two subpopulations of receptors (hypocretin-1 and hypocretin-2) with distinct affinities for the hypocretin peptides.[21]

The hypocretin system regulates the sleep-wake cycle, feeding behaviors, locomotion, reward behavior, autonomic nervous system activity, and the hypophysis-pituitary-adrenal axis.[21-23]

Anatomo-pathological studies in narcoleptic individuals with cataplexy show a specific loss of hypocretinergic neurons (Figure 1). The neuronal loss in narcoleptic individuals with cataplexy is selective, affecting only hypocretinergic cells and sparing the adjacent neighboring neurons that contain melanin concentrating hormone (MCH), which co-localize with hypocretinergic cells.[25]

2) Narcolepsy-cataplexy and hypocretins

Hypocretin deficiency engenders a state of disorganization and instability of sleep and wakefulness states. Excessive sleepiness, intrusions of sleep into wakefulness and of wakefulness during sleep (nocturnal sleep and naps), fragmented sleep, and innumerable transitions between sleep-wake-sleep have been reported. Dissociative phenomena of REM sleep – cataplexy, sleep paralysis, hypnagogic hallucinations, and REM sleep without atonia (RWA) have also been reported in subjects with narcolepsy.[20-24]

3) Autoimmune hypothalamic lesions and narcolepsy

Data supporting the autoimmune etiology of sporadic idiopathic narcolepsy-cataplexy:

• the presence of HLA-DQB1*0602 and polymorphism in the T-cell receptor alpha *(TRA)* gene confer a genetic susceptibility risk for the development of irreversible and selective post-natal injury to hypocretinergic neurons;[17,26,27]

• narcolepsy sporadically co-occurs with multiple sclerosis, also an autoimmune illness associated with HLA-DQB1*0602;

• there is an association between narcolepsy and autoimmune paraneoplastic syndromes, such as limbic encephalitis, with anti-Ma2 antibodies;[22-24,27]

• there is no clinically significant progression of symptoms, a fact incompatible with a neurodegenerative illness with progressive neuronal loss;[22-24,27]

• some patients even experience an improvement of symptoms with time, which is suggestive of a non-degenerative illness;[22-24,27]

• in some cases of recent-onset narcolepsy patients had elevated anti-streptolysin O (ASLO) titers, suggestive of recent streptococci infection. Such an infection could be an environmental trigger of an autoimmune reaction mediated by T-cell receptor alpha lymphocytes with antibodies against hypocretin cells;[26]

• there is selective destruction of hypocretinic neurons, sparing the Melanin-Concentrating-Hormone (MCH) positive cells located in the same anatomical region as hypocretin neurons;[27]

• intravenous administration of immunoglobulin G produces partial clinical response in some cases of recent-onset narcolepsy;[26]

• narcoleptic dogs present partial response to traditional immunosuppressant agents, such as methotrexate, azathioprine or prednisone, thereby delaying the onset of the disease.[26-27]

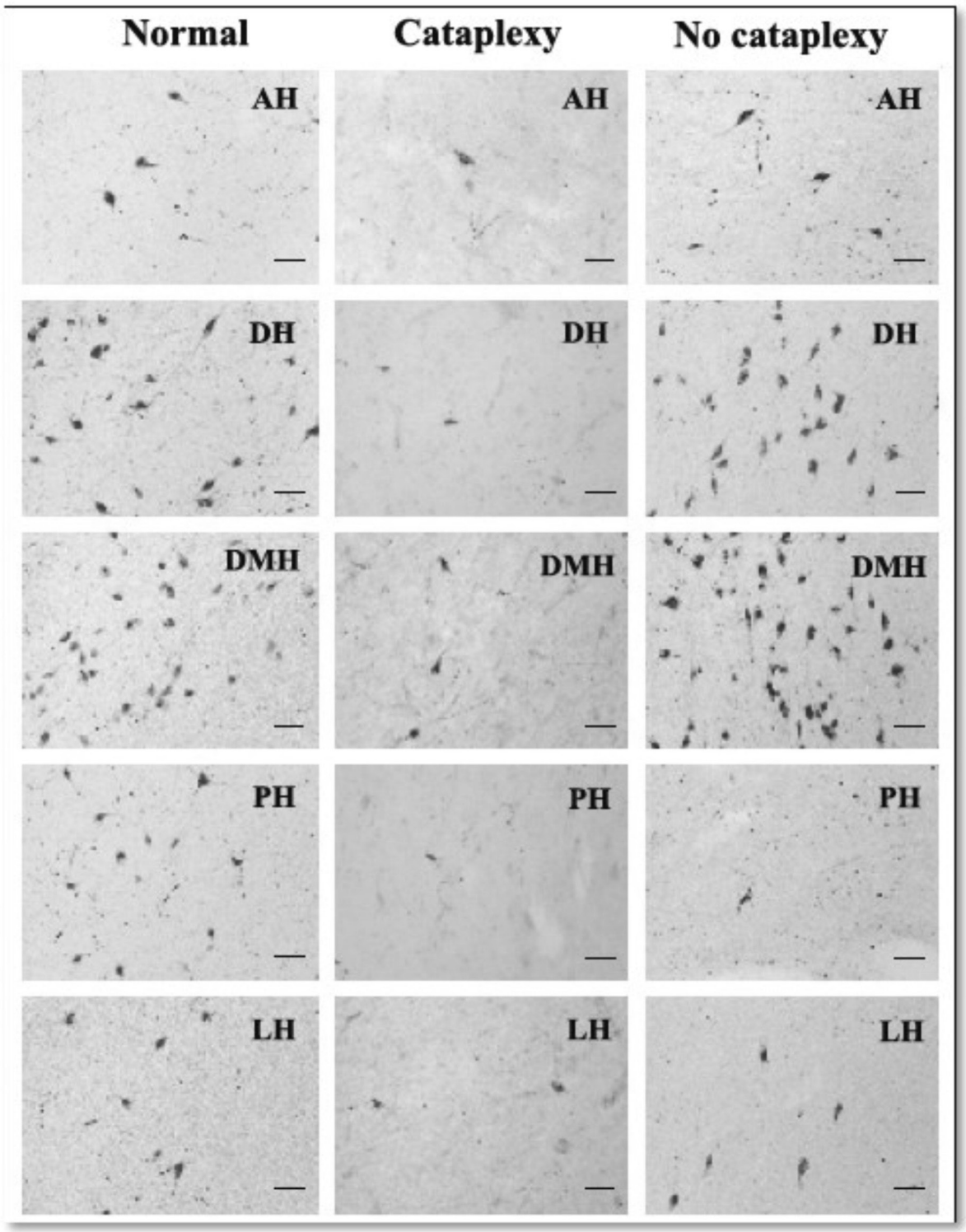

Figure 1 – Hypocretinergic neurons in the hypothalamic nuclei of healthy controls and narcolepsy patients (with and without cataplexy). In narcolepsy patients with cataplexy, neuronal loss was observed in the AH, DH, DMH, PH, and LH. In narcolepsy patients without cataplexy, neuronal loss was limited to the PH and LH (*AH = anterior hipothalamus; DH = dorsal hypothalamus; DMH = dorsalmedial hypothalamus; PH = posterior hypothalamus; and LH = lateral hypothalamus. Adapted under permission from Thannickal et al.*[25])

5. Complications

1) Quality of life and social, academic, and professional performance

Daytime sleepiness is the main cause of poor quality of life and cataplexy is an important limiting factor in the functioning of the narcoleptic individual.[28,29] Unlike other neurological conditions that affect sleep such as Parkinson's disease and obstructive sleep apnea syndrome, narcolepsy (and the side effects of its treatment) occur at an early age, impairing the patient during the period of academic learning and development of personality.[28,29]

Professional difficulties such as low income, loss of promotions, layoffs, unemployment, and especially academic dysfunction occur as a result of narcolepsy.[28,29] Side effects of narcoleptic medications such as orthostatic hypotension, dry mouth, and erectile dysfunction are additional setbacks that impair quality of life.[28,29]

2) Risk of automobile and industrial accidents

Excessive sleepiness increases the risk of automobile and industrial accidents specifically in the population under 40 years of age. In a driving-simulation test, narcoleptics were significantly more error-prone and the number of errors progressively increased throughout the duration of the test.[30,31]

6. Comorbidities

1) Depression

Between 18% and 57% of patients with narcolepsy are reported to have symptoms of depressed mood, loss of interest, and anhedonia; however, the prevalence of depression among narcoleptics is equal to that of the general population.[32] The reduction in quality of life due to diurnal sleepiness, isolation and social impairment and the cognitive deficits that occur in narcoleptics are key factors for the development of depressive symptoms.[32]

2) Anxiety

The prevalence of anxiety symptoms, panic attacks, and social phobia is about 25% and occur regardless of age and of the duration of the clinical treatment.[32] Anxiety, panic attacks, and social phobia are reasonable consequences of the chronic nature of the disease and are examples of the limitations imposed by narcolepsy onto the patients' social and professional outcomes. [32]

3) REM sleep behavior disorder (RBD)

The prevalence of RBD among narcoleptic patients ranges between 36% and 61%.

RBD in narcoleptic patients is clinically different from RBD not associated with narcolepsy. Among narcoleptics, RBD onset occurs earlier in life (about 31 years of age) and with slightly higher rates among men. There is no evidence that RBD associated with narcolepsy represents a risk factor for the development of neurodegenerative conditions.[33-37]

4) Eating disorders

The prevalence of compulsive eating and restrictive eating behaviors is greater in the population with narcolepsy than in the general population.[38] The symptoms of eating disorders do not correlate with medication use or with affective symptoms.[38]

5) Obesity

Obesity is more prevalent in patients with early-onset narcolepsy and in patients with more intense sleepiness, regardless of the use of medications. Obesity in the narcolepsy population is of the central type. The body mass index of narcoleptics is 10% to 20% higher than that of normal controls.[39] The causes of obesity might be related to the hypocretinergic neurotransmission, autonomic nervous system activity, basal metabolism, and the leptin-ghrelin system that is responsible for signaling caloric need, appetite, and satiety.[39-41]

6) Obstructive sleep apnea syndrome (OSAS)

The prevalence of OSAS is higher in the narcoleptic population (prevalence rates from 9% to 19%) than in the general population.[42]

7) Migraine

The prevalence of migrainous headaches in women and men affected by narcolepsy with cataplexy is 44% and 28%, respectively. The prevalence of migraines is greater in the narcoleptic subpopulation with more intense symptoms.[43,44]

8) Narcolepsy and multiple sclerosis

Narcolepsy and multiple sclerosis (MS) are both commonly associated with mutations of the HLA 0602 allele, and both are considered autoimmune disorders. Multiple sclerosis is a risk factor for narcolepsy, but the opposite is not true.[45]

7. Differential diagnosis

1) The differential diagnosis of ES includes:[1,46]

- behaviorally-induced insufficient sleep syndrome;
- obstructive sleep apnea syndrome;
- idiopathic hypersomnia of the central nervous system;
- hypersomnia associated with central nervous system disorders;
- hypersomnia due to associated medical conditions;
- hypersomnia associated with drugs or other substances;
- recurrent hypersomnia; and
- circadian rhythm alterations.

The presence of cataplexy and secondary symptoms, the age at onset, and the characteristics of naps are important for the differential diagnosis.

2) Behaviorally-induced insufficient sleep syndrome

Voluntary chronic deprivation of sleep generates more constant ES symptoms and in contrast with the irresistibility of narcolepsy sleep attacks, patients with insufficient sleep syndrome wish to sleep. Naps are long and relieving and ES disappears. The diagnosis is reached through the medical history, a sleep diary, and by the length of the sleep period.[46]

3) Obstructive sleep apnea syndrome (OSAS)

OSAS and narcolepsy can coexist due to the frequency of central-type obesity in the two conditions. The diagnosis is made through the medical history, polysomnography, and a multiple sleep latency test. The sleep fragmentation caused by apnea may mimic the classic narcolepsy changes in the polysomnography and in the multiple sleep latency test. Eventually, the definitive diagnosis can be reached only when OSAS treatment unmasks the sleepiness caused by narcolepsy.[46]

4) Idiopathic hypersomnia of the central nervous system

Distinguishing between narcolepsy without cataplexy and idiopathic sleepiness of the CNS is intrinsically difficult.[1,45] Narcolepsy naps are short, refreshing, occur in the form of attacks, and are not preceded by a significant degree of sleepiness. Idiopathic hypersomnia naps are long, non-restorative and preceded by a long-standing sleepiness sensation. Long, non-restorative nocturnal sleep (> 10 hours), morning fatigue upon waking, and episodes of sleep-drunkenness with mental confusion are characteristic of idiopathic hypersomnia rather than narcolepsy. Classic REM sleep abnormalities in polysomnography and the multiple sleep latency test do not usually occur in idiopathic hypersomnia of the CNS.[1,47]

5) Recurrent hypersomnia

Excessive sleepiness can occur in recurrent hypersomnia as in Kleine-Levin syndrome that is characterized by self-limited outbreaks lasting between 8 and 15 days associated with sleepiness, hyperphagia, copropraxia, coprolalia, and hypersexuality.[48]

6) Differential diagnosis of cataplexy

Medical conditions with episodes that mimic recurrent cataplexy attacks are very rare. Some findings that are present during a cataplexy attack and that significantly assist in the differential diagnosis are:

- Deep tendon areflexia during the transient attack;
- preservation of consciousness;
- absence of amnesia;
- maintenance of the auditory capacity and understanding during the attack;
- attacks triggered by laughter, excitement or fright; and
- sudden ending of the attack without amnesia or mental confusion.

7) Cataplexy and epilepsy

Cataplexy and sleep paralysis can be confounded with the diagnosis of astatic- or akinetic-type epileptic seizures.[49,50]

8) Cataplexy and gelastic seizures

Despite the occurrence of laughter during gelastic seizures and the relationship between laughter and cataplexy, there is no loss of neuromuscular tone or mental confusion during gelastic seizures.[50]

9) Hereditary diseases with isolated cataplectic-type attacks

Cataplexy attacks can occur in Type C Niemann-Pick disease, Norrie disease, Coffin Lowry syndrome, and Moebius syndrome.[23,51]

10) Pseudo-cataplexy

Pseudo-cataplexy is the simulation of cataplexy attacks by narcoleptic patients to acquire access to stimulant medication or some other form of compensation.[52]

11) Differential diagnosis of hallucinations in narcolepsy

a) Schizophrenia

Hallucinations in schizophrenia are mainly auditory, occurring while awake, while narcoleptic hallucinations are visual and assume the form of figures, shadows, and seeing in black and white and occur during transitions between sleep and waking.[53] The narcoleptic patient does not believe that the visions are hallucinations.[54]

12) Differential diagnosis of sleep paralysis

The prevalence of sleep paralysis in the general population is 2.5% to 40%. Sleep paralysis can be associated with the use of anxiolytic medication, medical illness, bipolar disorder, and unrestored sleep. [55]

8. Narcolepsy secondary to medical or neurological illnesses

More than 90% of narcolepsy cases are sporadic. Familial cases and cases of secondary narcolepsy are rare.[7] Secondary narcolepsy is associated with hypothalamic disorders, such as Type C Niemann-Pick disease, tumors, cranial trauma, multiple sclerosis, post-encephalitis, agenesis of the corpus callosum, sarcoidosis, neuro-cysticercosis, and limbic encephalitis. Narcolepsy-cataplexy is not associated with reduced hypocretin-1 levels in the CSF. In contrast, about 20% of head trauma cases are followed by chronically reduced CSF hypocretin-1 levels. Only a minority of TCE cases develop post-traumatic narcolepsy-cataplexy with PSG and MLST changes.[45,56]

9. Laboratory diagnosis of narcolepsy

1) Neurophysiological evaluation

The full neurophysiological evaluation of narcolepsy requires a hospital-based in-lab polysomnography (PSG) followed, on the next day, by the multiple sleep latency test (MSLT).[1] These tests must be completed under supervision of qualified technical staff and a qualified medical doctor[56,57] and require technical accuracy to avoid false negative or false positive results.[58] The following steps should be taken to ensure optimal sleep studies:

- discontinuation of all REM sleep-suppressing agents such as antidepressants (tricyclics, monoamine oxidase inhibitors, etc.) and CNS stimulants. The use of these medications must be suspended for a period of 14 days before the sleep studies (6 weeks in the case of fluoxetine);
- stop all sedatives, hypnotics, and antihistamine agents at least one week before the tests;
- reduce or remove stimulating substances such as caffeine and nicotine during the week preceding the examination; and
- maintain regular sleep-wakefulness schedules and sleep at least six hours per night during the two weeks prior to the sleep studies.

2) Polysomnography

a) Indication of PSG in narcolepsy

Polysomnography followed by the MSLT is mandatory for laboratory diagnosis in cases of narcolepsy without cataplexy (see below). In cases of well-characterized narcolepsy with cataplexy, PSG is still necessary for the diagnosis of comorbidities.[59]

Interpretation of PSG findings

The most frequent narcolepsy findings are:[60-62]

- normal sleep efficiency in younger patients;
- non-REM sleep latency below 10 minutes;
- reduction of REM sleep latency below 70 minutes;
- increased number of micro-arousals;
- increased transitions between sleep and waking stages;

• increased awake time after sleep onset (WASO); and
• increase of stage 1 sleep.

Other significant PSG findings include:
• increased eye movements during REM sleep;
• REM sleep without atonia (REMSWA); and
• increased phasic activity in the electroencephalogram (EEG).

These findings are more prevalent in the narcoleptic population than in the general population.[34,63,64]

3) Multiple sleep latency test

The MSLT must be performed according to the guidelines defined by the American Academy of Sleep Medicine task force.[65] A PSG carried out the night preceding the MSLT is necessary to document the nocturnal sleep quantity and to evaluate the sleep architecture.[65] The MSLT consists of five opportunities to sleep, taken every two hours during the main waking period.

a) MSLT indications

The MSLT is indicated for diagnostic confirmation in all patients who are suspected to have narcolepsy without cataplexy.[65]

b) Interpretation of the MSLT

An average sleep latency less than or equal to eight minutes with the presence of two or more REM sleep episodes is sufficient for the MSLT diagnosis of narcolepsy.[1]

The MSLT sensitivity and specificity are, respectively, 0.78 and 0.93 when using a cut-off point of two or more SOREMP episodes.[65] A negative MSLT for narcolepsy does not definitively discard the diagnosis.[65,66]

The SOREMP do not only occur in narcolepsy, it is thus important to consider and/or treat other illnesses before using the finding of SOREMP to support a narcolepsy diagnosis. Sleep fragmentation associated with OSA can cause false-positive results in the MSLT.[65,66]

c) Indications for MSLT repetition in narcolepsy:[67]

• first test affected by external circumstances or inadequate study conditions;
• ambiguous results (for example, only one SOREMP); and
• clinical suspicion of narcolepsy despite one or more previous negative MSLTs.

4) Maintenance of Wakefulness Test (MWT)

The MWT consists of a diurnal evaluation that measures one's capacity to remain awake in an environment with little sensory stimulation.[68,69] It is not a diagnostic test for narcolepsy and the American Academy of Sleep Medicine recommends the MWT to evaluate[65] the capacity of a patient to remain awake when there is a safety risk to the patient or others[66,67] and to determine the response to treatment in patients with ES [66,67]

5) Conclusions of the neurophysiological evaluation

The PSG and MSLT are useful to confirm the narcolepsy diagnosis. If PSG followed by the MSLT is negative on separate occasions, the diagnosis of ES due to narcolepsy is excluded.

6) Subjective evaluation of ES

The most widely used scale for the clinical evaluation of ES is the Epworth Sleepiness Scale[70] (Table 2). Values above 10 points are considered abnormal.[71,72]

Immuno-genetics and HLA-DQB1*0602 typing

Of the cases of narcolepsy with cataplexy, 88% to 98% are HLA-DQB1*0602 antigen positive.[7,12,13,73] However, the presence of this allele is not a sufficient or necessary factor for the development of narcolepsy.[7,73] In the general population, the prevalence of the HLA-DQB1*0602 antigen varies between 12% and 34%[8,14,15] (Table 1). In narcolepsy without cataplexy, the HLA-DQB1*0602 prevalence rate is 40% to 60%. [8,9] HLA typing therefore possesses

Table 2 - Epworth Sleepiness Scale

In the situations presented below, what is the probability of your "falling asleep" or of dozing off as opposed to simply feeling tired? Please answer based on your every-day life experience. Even if you have not experienced any of these situations, try to estimate how they would affect you.

Use the following scale to choose the most appropriate score for each situation:

0 = **no** possibility of falling asleep
1 = **small** possibility of falling asleep
2 = **moderate** possibility of falling asleep
3 = **high** possibility of falling asleep

SITUATION:	CHANCE OF FALLING ASLEEP:
Seated and reading	_____
Watching TV	_____
Seated in a public place (example: waiting room, church)	_____
Travelling one hour without stopping as a car, train, or bus passenger	_____
Lying down to rest in the afternoon when permitted	_____
Seated and talking with somebody	_____
Seated calmly after a lunch that did not include any alcohol	_____
If you have a car, while it is stopped for a few minutes in heavy traffic:	_____
TOTAL _____	

** Johns MW. A New Method for Measuring Daytime Sleepiness: The Epworth Sleepiness Scale. Sleep. 1991;14:540-5.*

low specificity in cases of narcolepsy without cataplexy and alone it is not sufficient to diagnose narcolepsy without cataplexy.[46,74] A positive HLA is a diagnostic support criterion, but its absence does not eliminate the presence of narcolepsy without cataplexy.

In conclusion, the clinical use of the HLA-DQB1*0602 allele for the purpose of diagnosing narcolepsy is limited because it possesses low sensitivity and specificity in patients without cataplexy [46,74]

Hypocretin type 1 in the CNS

The normal CSF hypocretin concentration is over 200pg/mL in all ages and across genders.[75-78] Hypocretin-1 levels below 110pg/mL are highly specific (99%) and sensitive (87-89%) for narcolepsy cases with cataplexy, but not sensitive for cases without cataplexy (Table 1). However, because 16% of the cases of narcolepsy without cataplexy are accompanied by lumbar hypocretin-1 levels above 110pg/mL, this finding does not exclude the diagnosis of narcolepsy without cataplexy.[79-81] A strong association exists between hypocretin-1 reduction in the CSF with the presence of cataplexy and positive HLA-DQB1*0602 haplotype.[13]

The measurement of hypocretin type 1 levels in the CSF is indicated in the following situations for the purpose of diagnosing sporadic narcolepsy:

- individuals with ES with one or more negative MSLT tests;
- when there are doubts regarding the existence of cataplexy;
- use of medication that is active in the CNS and could interfere with MSLT results;
- young patients (children and adolescents) without cataplexy; and
- patients who cannot complete the MSLT due to operational reasons.

In the situations above, HLA-DQB1*0602 typing must precede the measurement of hypocretin type 1 levels in the CSF. If HLA-DQB1*0602 is negative, it becomes unnecessary to measure hypocretin levels because there is no reduction of hypocretin type 1 in the CSF without HLA-DQB1*0602 positivity[46,74] in cases of sporadic narcolepsy.

Conclusion

It is the intention of the authors that the data presented herein will serve to help the growing number of health professionals establish accurate narcolepsy diagnoses, thus enabling the determination of the most adequate treatment. Perhaps, in future studies, the data herein will also serve the purpose of elucidating yet unknown mechanisms that underlie the complex chemical orchestrations that govern sleep.

Disclosures

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** Modest*
*** Significant*
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For more information, see Instructions for Authors.

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