

Revisiting Narcolepsy: The Practical Diagnosis and Mythology

Abstract^{a1}

Narcolepsy is a chronic neurological condition with impairments of the sleep-wake cycle. Narcolepsy manifests with four symptoms, the so-called classical tetrad:

- a) Episodic irrepressible uncontrollable Day-Time Sleepiness (DTS) is the key feature, and
- b) Abnormal bilateral episodes of muscle tone loss with clear consciousness (cataplexy) make the diagnosis definitive. Common but not necessarily required symptoms are
- c) Sleep onset distortions (hypnagogic hallucinations), and
- d) Awareness of being paralyzed when waking during the night (sleep paralysis).

^{a1}This series of articles focuses on the areas where the mythology may need to be broken and where limitations may not necessarily be recognized. This article has several parts, each interrelated yet independent. As with all publications, information such as this must be considered only after consultation with physicians and any medical information recorded here should not substitute for such consultations.

Diplopia and nocturnal insomnia are two other often ignored common symptoms.

The classical standard narcolepsy research criteria confirming a narcolepsy diagnosis consist of either a positive multiple sleep-latency tests (MSLT), or an abnormally low cerebrospinal fluid (CSF) Orexin (hypocretin) level. I focus on some controversies:

- a) a) First, the genes for narcolepsy have been largely ignored when applying the recognized criteria for diagnosing narcolepsy. These genes include particularly DQB1*06:02. However, the DQA1*01:02 gene should also be measured 1:02.
- b) Secondly, the multiple sleep-latency test (MSLT) may be overemphasized for definitive diagnosis, because the genetic test is as important or even more relevant. This is pertinent because, in the USA, insurance approval of costly medications such as modafinil, armodafinil and sodium oxybate are often dependent on the insurances applying a positive MSLT as a requirement; when it is negative, the insurances might tragically deny coverage of these medications: This might deprive many in the narcolepsy population of their essential life-sustaining treatment, even though they might have definite clinical features plus the gene expression, and often, already, response to wakefulness drugs.

Review Article

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c) Third, clinical evaluations must be standardized. At this stage, we, at the PNI ^{b2} apply modifications of the Epworth Sleepiness Scale in conjunction with the Fatigue Severity Scale, and the Neppe Narcolepsy Questionnaire, as fundamental ways to evaluate narcolepsy clinically. These historical rankings and screens combined with proper HLA screening may be adequate for more than 90% of diagnoses.

d) Fourth, the comorbidities of narcolepsy might include psychosis, anxiety, depression, impaired functioning, and seizure phenomena. These may reflect multifactorial etiologies: some of these may be linked with narcolepsy, and others unassociated.

I suggest a new model of hypocretin deficiency being slightly down-stream from the actual cause of narcolepsy-cataplexy. This accentuates the need for proposing two new terms, namely "primary narcolepsy" for the most common narcolepsy condition that appears to be hypothalamically linked to an auto-immune process involving hypocretin, and "symptomatic narcolepsy" due to infectious or tumor or trauma events involving the hypocretin / reticular activating system/ hypothalamus. On the others hand, some

^b "PNI" refers to the Pacific Neuropsychiatric Institute in Seattle, WA. "We" is used here to include application at the PNI; "we" is also used generically, for example, in broader recognitions of symptoms by researchers.

old classifications have used the previous terms “Type 1 Narcolepsy” for narcolepsy with cataplexy, and “Type 2 Narcolepsy” for narcolepsy without demonstrated cataplexy; this classification appears redundant and has ambiguities (e.g. some require proof by MSTL or Orexin levels and some do not). The various ICSD and DSM criteria are re-examined.

Keywords: Age; Armodafinil; Auto-Immune; Bilateral; Bipolarity; Cataplexy; Cerebrospinal Fluid; Children; CSF; Crying; Day-Time Sleepiness; Diplopia; DSM-V; DTS; Dyssomnia; EEG; Ego-Boundary; Emotion; Episodes; Epworth Sleepiness Scale; ESS; False Negative; False Positive; FISS; FISS-1; FISS-2; Gold Standard; HLA; HLA DR; DQB2 06:02; HLA-DQ6; DQA1*01:02; DQB1*06:02; Hallucination; HCRT; H1N1; Hypersomnia; Hypothalamus; Hypnagogic Hallucinations; Hypnopompic Hallucinations; Hypocretin; Hypocretin (Orexin); Neuropeptide Precursor; ICSD; Illusion; International Classification of Sleep Disorders; Laughing; Loci; Modafinil; Modified Epworth Sleepiness Scale; MESS; “Multiple Sleep-Latency Test”; Muscle Tone; Mythology; Narcolepsy; Narcolepsy Type 1; Narcolepsy Type 2; Neppe; Neppe Narcolepsy Questionnaire; NNQ; NNQ-4R; Neuro-Excitatory; Neurological; Neuropsychiatry; Nocturnal Polysomnography; Nortriptyline; NPSG; Nuvigil; Oxybate; OSA; Orexin; Periodic Leg Movements; PLM; Pharmacological Responsiveness; PNI Modified Fatigue Severity Scale; Primary Narcolepsy; Provigil; Rapid Eye Movement; RAS; Reticular Activating System, REM; Schizophrenia; Sleep; Sleep Apnea; Sleep-Onset; Sleep-Onset REM Period; Seizure; SOREMP; Sleep Paralysis; Sleep-Wake Cycle; Symptomatic Narcolepsy; Tetrad; Transition; Tricyclic; Uncontrollable Sleepiness; Venlafaxine; Wakefulness; Weakness; Xyrem

Narcolepsy: The condition: Part 1

The classic clinical tetrad

Narcolepsy is a chronic neurological condition resulting from impairments of the sleep-wake cycle, in which patients necessarily uncontrollably fall asleep during the day. (Day Time Sleepiness or DTS). They might also often have symptoms pertaining to abnormal muscle tone episodes (cataplexy). When the DTS is combined with the cataplexy, the clinical diagnosis is definitive. There are two other frequent symptoms, namely sleep onset distortions (“hypnagogic hallucinations”), and waking up during the night from sleep and experiencing paralysis (“sleep paralysis”).

Day-time sleepiness (DTS) involves recurrent periods of an irrepressible need to sleep: This is uncontrollable and even may occur while driving, when patients learn to quickly go to the side of the road, but where they are at major risk for car accidents. They then lapse into sleep, and they may nap several times within the same day.

Cataplexy involves brief episodes of sudden bilateral loss of muscle tone, most often linked with intense emotion.

This therefore constitutes the classical clinical Narcolepsy tetrad (four major symptoms) of:

- i) Day time sleepiness (DTS) and cataplexy, particularly,

- ii) Plus the two other accessory features of hypnagogic hallucinations and sleep paralysis.

These two accessory features are, at times, elicited and sometimes documented, even at a lab level, but they are clinically pertinent, though often neglected.

Standard criteria

The standard research criteria applied to confirm a narcolepsy diagnosis consist of either the multiple sleep-latency test (MSLT), and / or measures of cerebrospinal fluid (CSF) Orexin.

The data in this Part 1 points to some key information, yet because it is highly concentrated, some concepts may seem difficult to follow, at this point. But this broad overview might provide a perspective when later on I cover each concept in more detail and accentuate two key points:

- i) I illustrate specifically a controversy of the gene for narcolepsy largely being ignored, even in the criteria for narcolepsy, and yet a possible overvaluation of multiple sleep-latency test (MSLT) sleep tracings being used for definitive diagnosis. This is important because in the USA insurance approval of expensive medications is often dependent on the MSLT being positive and when negative it might deprive many in the population of essential life-sustaining treatment.
- ii) I also emphasize the need for clinical evaluations to be standardized, and point to modifications of the Epworth Sleepiness Scale in conjunction with the Fatigue Severity Scale, and the Neppe Narcolepsy Questionnaire.

Genes

The usual clinician does not have access to such specialized tests, yet every clinician can ask for the Narcolepsy gene test (e.g. the main one is HLA DR DQB2 06:02), and this correlates very highly with Orexin in narcoleptic patients (90% or higher e.g. 92%) [1,2]. The problem is it has false positives in about one tenth to one third of patients depending on the population.

In our clinical experience spanning over two decades of evaluating such narcolepsy patients, these false positives expressing the narcolepsy gene (usually “DQB 06:02”) are not just “control” normal patients. Every one of these controls in our neuropsychiatric population, has had some kind of sleep disturbance. But detailed history shows that these “controls” exhibit lifelong symptoms of different sleep disorders though not clinical narcolepsy. Because other symptoms like depression or anxiety may not be sufficient in many of these cases, it is that likely that many of these patients have other “primary dyssomnias” and often such conditions have not been well delineated. Yet, commonly the families of these “controls with positive narcolepsy gene expression”, have classical narcolepsy, also with their HLA “DQB 06:02” gene being expressed.

The utility of genetic testing for narcolepsy was recognized even by 2002 [3], and the specific HLA DR2 “narcolepsy” gene was reported in 1984 [4,5].

But narcolepsy gene testing has remained extremely under-rated by many experts who have preferred the far more expensive,

specialized, and time-consuming “multiple sleep-latency test” (MSLT) test instead. Yet, in our experience, the HLA typing for the narcolepsy gene can be performed as a simple genetic blood test that provides powerful confirmatory data when used as an addition to the clinical data. Indeed, in our experience the gene plus clinical data, as shown later in this article, provides as strong or even stronger diagnostic support than the MSLT test.

More complex testing

Whereas the sleep-onset MSLT, and the Orexin CSF tests are valuable to have available as extras in cases of further diagnostic query after detailed clinical plus gene evaluation, they are specialized because of their costs (MSLT) or invasiveness (CSF) and require specialty involvements.

I know now that narcolepsy is regarded as due to Orexin deficiency [1] in the hypothalamus. This may or may not be an auto-immune process, as sometimes trauma or infection can induce it in predisposed individuals. But that can only be measured using cerebrospinal fluid: So this is not something easily accessible to many clinicians.

Orexin deficiency correlates strongly with the most commonly used standard sleep lab test, the MSLT (possibly 95% ref). The MSLT involves a measure of how often patients go directly into rapid eye movement sleep within say 8 minutes of going to sleep during the day under standard precautions. This is an expensive test, but when it is positive and applied with all its required stringencies, such as not having sleep for (say) six hours before, and not having taken confounding medication, it provides strong support for the diagnosis the narcoleptic condition. Moreover, the MSLT can be applied sequentially to monitor medication responses.. But, there is commonly a tragic problem in the USA. When the MSLT results are negative and yet the clinician based on structured questionnaires, gene testing and pharmacological response regards the narcolepsy diagnosis as definite because these same patients may not be authorized to receive their very expensive wakefulness medications from the insurance company. This is because the insurance industry have taken the criteria of diagnosis of MSLT as the most definitive.

A negative MSLT, in the presence of positive other testing and even medication sample response, is not a rarity, unfortunately, in our experience. This is because only slightly more than one fifth of narcoleptics have a positive MSLT on the first run of the test [6]: Usually 2 such positive tests out of four, five or six, are required. Moreover, some researchers that there are false positive MSLT results: Depending on the population this may be as much as about 3 in 10 positive MSLT cases not even having narcolepsy [7].

Positive MSLT test results vary with age, specific symptoms in populations, and other confounding factors [1,8]. Yet, proponents of the MSLT, and this includes most sleep laboratories, claims the MSLT is the most definitive test for narcolepsy, so that this is conflict with the above:

The data suggests that the MSLT cannot be used purely in isolation to confirm or exclude narcolepsy. Many experts believe it is now indicated only in selected patients with excessive daytime sleepiness. And almost every specialist agrees it is most valuable when interpreted in conjunction with clinical findings [7]. It may

be that a useful, but as yet unperformed definitive controlled study would be the proportion of patients expressing Clinical features plus HLA-DQ2-06:02 typing who have positive MSLTs and what proportion are of MSLT patients do not express any of the implicated HLA-DQA and DQB genes.

Age

Narcolepsy usually has an onset at an early age (childhood, adolescence or young adulthood), but is often missed till late [9], the mean delay to diagnosis is up to 15 years, with rare individual cases being delayed even for 60 years, though with education, there might now be a shorter delay to diagnosis.

The delay in diagnosing narcolepsy may sometimes be linked with the frequent association with other sleep-wake disorders [10].

In my opinion, many cases are never diagnosed. Misdiagnosis or absence of diagnosis is a key problem. Early diagnosis of narcolepsy has the possibility to offer affected persons an adequate medication to lead an almost normal life and the future possibility to cure narcolepsy through immunomodulation therapy [10].

Comorbidity

Lack of symptom recognition is unfortunate, because narcolepsy has a high comorbidity burden. Many disorders manifest with symptoms that overlap with narcolepsy and patients are labeled bipolar, schizophrenic, depressed and anxious. These detrimental effects impact on proper health-care being used, employment, and quality of life. Education and awareness of narcolepsy and its symptoms might assist [9].

Moreover, particularly in the young, the symptoms can be disabling enough to interfere with functioning of the child, and therefore compromise his/her education. That in turn leads to further stigmata and impairments.

Men and women have very similar narcolepsy related symptoms. But women may be more likely to be diagnosed later: 85% of men were diagnosed by 16 years after symptom onset (still a long time), compared to a 28 year delay in women (a very long time). One wonders whether the large gray area are those who are undiagnosed [11].

Interestingly, despite being more objectively sleepy (e.g. on MSLT), women were far less likely to report lifestyle impairments in the areas of personal relationships and physical activity, but were also slightly more likely to self-medicate with caffeine [11].

However, most important may be a way for clinicians to easily and cheaply make the diagnosis clinically without having to resort to tests such as MSLT, and CSF Orexin levels.

This is what this paper is about.

Gold standards

No real gold standard currently exists for the diagnosis of narcolepsy. Conventional diagnostic criteria are unwieldy and arbitrary. Clearly defined criteria for case selection are needed to compare the results of different studies [3].

However, these criteria require highly specialized evaluations, and therefore are limiting.

Currently, the *International Classification of Sleep Disorders (ICSD) Revised 4* represents the research “gold standard” for the diagnosis of narcolepsy. It begins with the classical association of recurrent daytime naps and cataplexy and this has now become sufficient for a definite diagnosis, because the cataplexy symptom is so specific.

But there are many patients without cataplexy, who have daytime sleepiness and other associated features. In a specialized setting, sleep studies may greatly contribute.

The criteria have changed minimally over the years. For example, in DSM 4TR is very close [12]. DSM-V [13] has improved this a little and now recognizes Sleep Paralysis. It also emphasizes co-morbidity of Narcolepsy diagnoses with Schizophrenia and Bipolarity. Whereas, in my opinion, this might be true, it also might not be, because narcolepsy experiences manifest in different ways and may be misdiagnosed. One measure may be pharmacological responsiveness to appropriate neuroleptic, for example, in appropriate dosage [14,15].

However, the linkage may be pertinent, as well, in some patients:

Preliminarily, there is a higher frequency of DQB1(*)-03:01/06:02 antigens in N-C children with narcolepsy and cataplexy who develop what Huang is calling “secondary schizophrenia”. This linkage is a therapeutic challenge where there may be long-term persistence of severe psychotic symptoms [16].

Importantly, diagnoses are also by exclusion so DSM 4R included, as it does for almost every other condition: The classic phrase for all Diagnostic and Statistical Manual of Mental Disorders comments is: “The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or another general medical condition”.

Interestingly, at one point, we spoke of narcolepsy, type 1 (with cataplexy) and narcolepsy, type 2 (without). This is really extra verbiage, unnecessary particularly as some have tried to suggest special criteria for qualifying for Type 1 and Type 2-eventually very few would qualify.

Let’s now list minima that are usually mentioned

Remarkably there are amazing omissions such as sleep paralysis in the clinical DSM criteria and genetic components in the ICSD criteria. Let’s examine this in the light of recent history:

1. Day-time sleepiness frequency at minimum should be at least three times per week over the past 3 months.
2. The presence of at least one of real cataplexy or cataplexy equivalent in children should occur at least a few times per month:
 - a. In individuals with long-standing disease, cataplectic events can be brief (seconds to minutes) episodes of sudden bilateral loss of muscle tone with maintained consciousness that are precipitated by laughter or joking.
 - b. In children or in individuals within 6 months of onset, spontaneous grimaces, or jaw-opening episodes with tongue, thrusting or a global hypotonia, without any obvious emotional triggers, are allowed.
3. Recurrent intrusions of elements of rapid eye movement (REM) sleep into the transition between sleep and wakefulness, as manifested by either hypnopompic or hypnagogic hallucinations or sleep at the beginning or end of sleep episodes
4. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or another general medical condition.

Table 1A: Criteria for Narcolepsy [12].

a) The International Classification of Sleep Disorders (ICSD) ICSD 4R

ICSD 4R is the current gold standard for the diagnosis of narcolepsy and reflects the criteria for the sleep association.

The classical association of recurrent daytime naps and cataplexy is sufficient for a definite diagnosis, the latter symptom being specific. *That appears logical.*

However, there is a wide spectrum of cases without cataplexy, where daytime sleepiness and other associated features are evocative but not specific, then according to the ICSD polysomnographic studies are mandatory. As you will see in this paper, with due respect, *I regard, in a clinical practice, genetic studies as not only adequate, but mandatory with or without Polysomnography.*

347.00 (G47.419) Narcolepsy without cataplexy but with hypocretin deficiency: Criterion B requirements of low CSF hypocretin-1 levels and positive polysomnography/ multiple sleep latency test are met, but no cataplexy is present (Criterion B1 not met). NOTE there is no mention of genetics!

347.01 (G47.411) Narcolepsy with cataplexy but without hypocretin deficiency: In this rare subtype (less than 5% of narcolepsy cases), Criterion B requirements of cataplexy and positive polysomnography/ multiple sleep latency test are met, but CSF hypocretin-1 levels are normal (Criterion B2 not met).

347.10 (G47.429) Narcolepsy secondary to another medical condition: This subtype is for narcolepsy that develops secondary to medical conditions that cause infectious (e.g., Whipple's disease, sarcoidosis), traumatic, or tumoral destruction of hypocretin neurons.

Additional modifiers

Mild: Infrequent cataplexy (less than once per week), need for naps only once or twice per day, and less disturbed nocturnal sleep.

Moderate: Cataplexy once daily or every few days, disturbed nocturnal sleep, and need for multiple naps daily.

Severe: Drug-resistant cataplexy with multiple attacks daily, nearly constant sleepiness, and disturbed nocturnal sleep (i.e., movements, insomnia, and vivid dreaming).

Table 1B: ICD 9 and ICD 10 diagnoses.

There are confounders with sleepiness in patients with narcolepsy without cataplexy, idiopathic hypersomnia, and Obstructive Sleep Apnea Syndrome creating needs for Interobserver Reliability in the ICSD Diagnostic Criteria for Narcolepsy [17].

The ICSD-3 of 2014 provides new terminology, classifications, and diagnoses for this disorder that's characterized by daily periods of irrepressible need to sleep or daytime lapses into sleep. This change was made because some patients demonstrate what they consider the fundamental cause for narcolepsy type 1 namely hypocretin deficiency but without cataplexy. The data presented in this article may suggest however that that fundamental cause is an early result of hypothalamic change and that the genetic elements may even be more relevant to causality. I do not see this classification as bringing anything further to the table, except limiting the diagnosis profoundly to MSLT, polysomnography and

CSF Orexin, and possibly incorrectly excluding genetic testing, or even pharmacological responsiveness, and excluding most of the population with narcolepsy because they do not qualify on testing.

However, this classification at least widens clinical criteria to include both daily periods of irrepressible need to sleep or daytime lapses into sleep, but may narrow patient diagnosis, in terms of episodes not being daily. This to me, with respect, is problematic.

The ICSD has revised the classification of narcolepsy and this is more sensible: ICSD Revised 4 represents the new gold standard for the diagnosis of narcolepsy. Now the classical association of recurrent daytime naps and cataplexy is sufficient for a definite diagnosis, the latter symptom being specific. On the other hand, if there is doubt, in the wide spectrum of cases without cataplexy, where daytime sleepiness and other associated features are

elicited, but not specific, polysomnographic studies are then mandatory.

We can go back in time: There is an extended history across these cultures attributing these symptoms to supernatural causes. These involve entities “incubi” dating back to the times of Martin Luther, or the Newfoundland “Ag-Rog” or “Old Hag” or by the 1970s, “alien abduction”. This mythology is usually linked to nocturnal sleep episodes either the sleep paralysis which is non-specific and not diagnostic, or the hypnagogic (sleep-onset) or hypnopompic (sleep awakening) hallucinatory experiences. This may lead to further distressing dynamics, and these beliefs might partly relate to the “true nightmare” [18]. Interestingly, these kinds of interpretations with altered consciousness are not unusual, particularly in a related episodic condition with defect of consciousness, epilepsy [19].

Narcolepsy: the key clinical features: Day-time sleepiness and cataplexy. Part 2

In this section, I discuss the two key features of Narcolepsy namely:

- i) Daytime Sleepiness and
- ii) Cataplexy

Without Daytime Sleepiness there can be no diagnosis of Narcolepsy. It is a sine qua non. There can be narcolepsy without cataplexy, and sometimes is in about a third of cases. % But if there is cataplexy, with classical Daytime Sleepiness the diagnosis effectively is indisputable.

Let’s examine both of these briefly:

Day Time Sleepiness (DTS)

Daytime sleepiness attacks in narcolepsy involve recurrent periods of an irrepressible need to sleep, lapsing into sleep, or napping occurring within the same day.

One description is “Irresistible attacks of refreshing sleep”. Another conceptualization is these attacks are short-lived. Frequently, they may last half an hour and then the patient is refractory to another such attack for several hours e.g. 2 hours. The patient After the DTS attack, the patient feels remarkably refreshed. An essential component of this classical DTS is the episodic element. That differentiates them from chronic maintained states of sleepiness.

The minimum frequency varies for these to be considered narcoleptic: The ICSD requires occurrence at least three times per week over the past 3 months. DSM 4 R required at least daily. More pertinent may be the associated activities: For example, post-prandially an hour after a high carbohydrate lunch, patients prone to hypoglycemia may become sleepy.

Clinically, in narcolepsy, I distinguish between physical tiredness and true uncontrolled daytime sleepiness with the onset or REM sleep.

Nuggets

- i) The patient still only sleeps 7 or 8 hours per 24 hours. This means patients have insomnia at night. They do not sleep 7-8 hours at night but less to make up for their micro-sleeps during the day. Narcolepsy is often classified, in my opinion incorrectly, as a “hypersomnia”. This would refer to a disorder of increased sleep in the 24-hour day. It is not a hypersomnia, but a “dyssomnia” with breakage of sleep distribution: the disorder of increasing short nap sleeps during the day is countered by insomnia at night to make up the 7 or 8 hours required for mean sleep during the 24-hour period.
- ii) Almost every narcoleptic I’ve seen has had motor vehicle accidents where they’ve fallen asleep. This is not quite as dangerous as seizure disorders with loss of consciousness when there is no warning. But narcoleptics often can pull over to the side of the road (a few seconds warning) but this is still dangerous, requires medical review, and unless the DTS is excellently controlled these patients should not be driving, and even if well-controlled should recognize that driving is their responsibility and should be for short trips only under medical and prescription supervision.
- iii) Therefore, when they take appropriate medicines e.g. Modafinil and Armodafinil they are much better and may not be dangerous. Epileptics are sometimes completely controlled on anti-convulsants and the criterion for driving there varies with jurisdictions e.g. 3, 6, or 12 months or doctor’s opinion.

How do I measure the DTS in a clinically standard way? The best way, I think, is applying two scales such as the Modified Epworth Sleepiness Scale (MESS) [20-22] with the PNI Fatigue Severity Scale (PFISS) [22]. If there are any clues to narcolepsy, such as a MESS score of 10 or more, with a FISS-1 score of 20 or less, we then apply a standardized questionnaire, such as The Neppe Narcolepsy Questionnaire (NNQ) [23-25]. These are discussed later.

Cataplexy

Cataplexy is a medical condition involving sudden and transient episodes of usually bilateral muscle weakness is accompanied by full conscious awareness. This is due to a sudden loss of muscle tone, and is most often associated with intense emotion (although there are exceptions). The fact that this is bilateral-on both right and left sides together-and occurs in clear consciousness, differentiates cataplexy from seizure disorders.

Cataplectic attacks vary in severity depending on the incident and the individual:

Sometimes cataplectic attacks involve sudden minimal weakness, such as barely perceptible slackening of the facial muscles; alternatively, a cataplectic attack might manifest marked physical collapse with loss of muscle tone and strength, where the body falls helplessly, though remaining conscious.

A basic diagnostic issue is that cataplectic attacks are almost invariably triggered by strong emotions such as laughing, crying, or terror.

Cataplexy affects about 70% of people who have narcolepsy [26]. Occasionally, cataplexy precedes the classical EDS. The extent of severity varies.

Cataplexy as a symptom is sometimes difficult to conceptualize. When trained, raters are “almost perfect” in observing the videotaped physical signs after training [17]. But ordinary mental health specialists don't have that training and don't see such attacks: Therefore a standardized question series such as the NNQ should be useful. Again the NNQ is valuable in this [23,24].

Cataplexy manifests as muscular weakness attacks that are brief, and most last from a few seconds to a couple of minutes.

Typically, attacks could involve any or all of dropping of the jaw, neck weakness, and/or buckling of the knees. Complete full-blown muscle paralysis with postural collapse may occur [27-29]. Speech may be slurred and vision may be impaired (double vision, inability to focus) [30], but hearing and awareness remain normal.

Cataplexy attacks are self-limiting and resolve without the need for acute medical intervention [27-29]. If the person is reclining or lying down comfortably, the patient may transition into one of the other narcoleptic features namely, sleepiness, hypnagogic hallucinations, or a sleep-onset REM period [31].

Cataplexy worsens with fatigue, and it might rarely not be triggered by the usual strong emotional reactions such as laughter, anger, surprise, awe, and embarrassment. Sudden physical effort may trigger it, and being caught unawares or off guard may trigger it or it may be quite spontaneous with no identifiable emotional trigger.

Cataplexy is very varied and more difficult to assess.

It varies from minimal muscle tone-hardly noticed, to major episodes e.g. drop attacks. It often is bilateral, on both sides. Cataplexy may develop only later, particularly when the narcolepsy begins, in children. The cataplexy does not respond as well to Modafinil and requires often something else, e.g. oxybate or tricycles or venlafaxine. Some patients try to avoid emotional situations and these may require prophylaxis.

Almost invariably cataplexy is associated with narcolepsy. Cataplexy without narcolepsy is rare and the cause is unknown.

Even in a collapse, people are usually able to avoid injury

because they learn to notice the feeling of the cataplectic attack approaching and the fall is usually slow and progressive. In children, cataplexy and muscle weakness episodes triggered by emotions such as laughing and joking are often atypical. They may be without triggers and affect the face with mouth opening, tongue protrusion. This might occur often with very abrupt sleepiness and weight gain.

As in REM sleep, the person continues to breathe and is able to control eye movements [32].

Cataplexy presence is almost diagnostic clinically for narcolepsy, yet I have seen a patient with definite cataplexy expressing the HLA DQB1 06:02 gene but with no classical daytime sleepiness, but severe chronic fatigue instead. It could be argued that the daytime sleepiness will come but the fatigue severity in the absence of other conditions is notable.

This would be an example of the value of using a standard clinical measure. The best way is applying a standardized questionnaire, such as The Neppe Narcolepsy Questionnaire (NNQ) [23-25]. These are discussed later.

Accessory features

Sleep paralysis is regarded as associated with REM sleep atonia intruding into wakefulness. This produces impaired maintenance of REM sleep atonia and might manifest with dream imagery intruding into wakefulness [33] at the start of sleep (e.g. hypnagogic hallucinations) and on awakening (hypnopompic hallucinations). In my opinion, these are often visual and sometimes illusory phenomena, but not hallucinations themselves as they are distortions, not images seen or voices that are heard without any sensory stimulation so the term “hallucination” may be inaccurate sometimes.

Associated features

Attention to periodic leg movements (PLM), sleep apnea and REM sleep behavior disorder (RBD) is particularly important in the management of the older narcoleptic patient, in whom these conditions are more likely to occur [33].

Differentiating fatigue and sleepiness. Part 3

Fatigue is a general term which refers to any of *exhaustion, tiredness, weariness, drowsiness, low energy, sleepiness during the day when you are supposed to be awake.*

At the PNI, we have used the PNI Fatigue Severity Scale (FISS) for about 2 decades and found it useful. It is a self-scored evaluation of fatigue designed to differentiate from clinical depression, as both share fatigue symptoms. However, it's also particularly useful as well in narcoleptics to differentiate from sleep apnea and other dyssomnias. We actually use it as part of a series of 10 tests that we call the Diagnostic-Screen 10. The Epworth is another one of these ten tests.

The ratings for the PNI Fatigue Severity Scale (FISS) are based on a 0 to 6 scale (our PNI scoring system) scored over the last week.

There are two tests.

The **FISS-1** previously just the Fatigue Severity Scale (FISS) contains 9 items so the minimum score is 0 and maximum is 6.

Range is therefore 0 from 54.

Scoring 10 or above is significant. 19 or above reflects problems.

The FISS-1 first item is different My motivation is lower when I am fatigued is scored as a subset decimal point.

Reference is <http://www.mult-sclerosis.org/fatigueseverityscale.html> but this scale uses a 1-7 range. This was the only test we used till 2012.

In 2012, the PNI added an accessory 5 point scale-the FISS-2 was added. This was based on feedback from patients and it could be regarded as the activation component. We sometimes combine the scores. This adds 30 more points to the score. We separate

the FISS-1 which is the official score, from the FISS-2 which is the extra item score. Our preliminary impression is the FISS-2 might correlate better with features such excessive daytime sleepiness, and also motivational features particularly on awakening. But this needs to be properly analyzed.

Surprisingly, I could not find studies of FISS (here the FISS-1) with ESS. Yet it is logical because patients with many causes for fatigue (systemic e.g., anemia, cardiac, renal, hepatic, Lyme disease; brain related e.g. sleep apnea; psychiatric e.g. depression, anxiety; general e.g. chronic fatigue syndrome) should have their higher FISS scores correlated with the ESS to measure comparative daytime sleepiness. The initial clue for going towards the NNQ is when ESS scores are >11 for narcolepsy daytime sleepiness and also fatigue is only mildly elevated (averaging 1 or 2 per item) as opposed to very high. We have found this clue valuable. As indicated, now, it looks like a relatively high FISS-2 score compared with FISS-1 may also provide an excellent clue to other ongoing investigations. With any of these clues being abnormally high, we then do the Narcolepsy gene blood screen.

There are other approaches as well. For example, The Sustained Attention to Response Task is a valid and easy-to-administer measure to assess treatment effects in narcolepsy, enhanced by combining it with the Epworth Sleepiness Scale [21].

PNI FATIGUE SEVERITY SCALE (FISS) (FISS-R 2012) © PNI 2012

Name: _____ **Date:** _____

Instructions: This questionnaire contains nine statements that attempt to explore the severity of fatigue symptoms.

Fatigue is a general term which refers to any of exhaustion, tiredness, weariness, drowsiness, low energy, sleepiness during the day when you are supposed to be awake.

Please read each statement and circle a number from 0 to 6. As a guide-line, base your answer on how you've felt over the last week.

A low value indicates that the statement is not very appropriate whereas a high value indicates agreement with the statement.

In the past week:

0 means "I do not have this" ;

1 = this is present but very mild or occasional;

2 = This has been mild;

3 = "This has been moderate";

4 = This has been moderately severe;

5 = This has been severe

6 = This has been extremely severe".

FISS -1 direct fatigue

1. My motivation is lower when I am fatigued	0	1	2	3	4	5	6
2. Exercise brings on my fatigue.	0	1	2	3	4	5	6
3. I am easily fatigued.	0	1	2	3	4	5	6
4. Fatigue interferes with my physical functioning.	0	1	2	3	4	5	6
5. Fatigue causes problems for me.	0	1	2	3	4	5	6
6. My fatigue prevents sustained physical functioning.	0	1	2	3	4	5	6
7. Fatigue interferes with carrying out certain duties and responsibilities.	0	1	2	3	4	5	6
8. Fatigue is among my three most disabling symptoms.	0	1	2	3	4	5	6
9. Fatigue interferes with my work, family, or social life.	0	1	2	3	4	5	6
FISS -1 total _____							
FISS-2 activation							
10. It is difficult for me to get out of bed in the morning.	0	1	2	3	4	5	6
11. It is difficult for me to get going in the morning.	0	1	2	3	4	5	6
12. I lack energy.	0	1	2	3	4	5	6
13. I lack enough energy to perform even routine tasks.	0	1	2	3	4	5	6
14. I have episodes of significant tiredness during the day.	0	1	2	3	4	5	6
FISS -2 total _____							
FISS Grand Total _____							

Measuring sleepiness

The Epworth sleepiness scale (MESS)

This is an 8 item self-scored report. It reflects how much patients fall asleep under normal circumstances, and it is sometimes based on imagining what would have happened.

The original measures on the Epworth Sleepiness Scale (ESS) that we first encountered was 1 (normal, never) to 4, but it appears that is seldom used today, though many publications don't describe what they're using.

We have scored based on 0 to 3 scores with 0= never, 1= slight, 2= moderate, 3= high chance of dozing. The original scale Statistical analysis is much easier when looking at 0 to 3, and this also helps "eyeball" results quickly.

However, we wanted to have a broader severity indication. Therefore we modified the ESS:

All our scoring is 0 for never and applies a 0 to 4 so we apply a 5-point scale. Range therefore 0 to 24. We still obtain two scores so our data can be compared with others using the ESS 0-3 scale.

Scores of 5 or above are clinically relevant. Scores of 8 to 10 reflect major symptoms.

Adapted from <http://www.stanford.edu/~dement/epworth.html>.

The Epworth Sleepiness Scale score calculates the presence of residual sleepiness. The key series of questions are: "Under normal circumstances, how likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? Even if you have not done some of these things recently, try to imagine how they would affect you. Use the following scale to choose the most appropriate number for each situation."

- 0 = would never doze: you never or almost never doze when that's happening
- 1 = Slight chance of dozing: you have a slight chance of dozing
- 2 = Moderate chance of dozing: you have a moderate chance of dozing
- 3 = High chance of dozing: you have a high chance of dozing
- 4 = always dozing: you're almost always dozing when that's happening

For statistical reasons, we obtain the 2 scores (based on the original 4 point scale of 0-3) MESS R3 and the MESS R4 score based on the later 5 point scale (0-4).

The data in the literature is exclusively the 4 point scale with a maximum of 8*3= 24.

It is here that scores of 11 or 12 are suggestive for narcolepsy particularly if the FISS-1 fatigue score is not very high (e.g. <20). But given that a score of 4 is relatively rare, and would most commonly push the items below 11 or 12, we could technically use MESS R4 in any event.

The MESS and FISS gives us the clue to ask the patient to complete the NNQ below, and whenever we do this for the first time, we perform HLA testing for narcolepsy.

These clinical tools help prioritize individuals with the most severe illness regarding whom we should prescribe medication for. They are not perfect but at least standardized for each patient. We consider polysomnography (PSG) but it is rare for this to be needed because more than 90% of our patients are clear-cut. Additionally, the modern media facilitate reaching out to the general population to raise awareness of the other conditions associated with EDS such as sleep apnea [34].

And it is this combination, Narcolepsy plus Sleep Apnea, that we see quite frequently.

We return to the ESS: There are over a hundred peer reviews publications on the Epworth in many countries, and translated into several languages.

1. There is good agreement on all the items totaled together between the patients and their close relatives, but not always within individual items.
2. The correlation of objective sleepiness as measured by the ESS and the close relatives is high, and this also correlates on MSLT [35].
3. The cut-off for EDS (MESS >10 points) was chosen in line with the traditional ESS.
4. Data scores before and after interventions correlated with improvement in predicting OSA in patients with COPD [36].
5. ESS answers differ according to sociocultural and economic conditions. For example, a score of 8 or higher on the ESS would seem a more appropriate cutoff score than 10 or 11, that many others use, to suspect clinically relevant sleepiness in the Turkish population [37].
6. Men and women reported similar degree of subjective sleepiness as measured by the Epworth Sleepiness Scale, though women demonstrated significantly more severe objective sleepiness on multiple sleep latency testing (MSLT) [11].
7. Epworth Sleepiness Scale scores appear to be an indication of personal sleep debt that varies depending on one's individual sleep requirement [38].
8. Interestingly, ESS scores were considerably more sensitive than MSLT scores in documenting efficacy of the most common treatment, modafinil [20] (and presumably, it would be the same for its very close cousin, armodafinil). On the other hand, the improvements in MSLT scores were minimal and remained in the pathologically sleepy range [20]. These findings suggest that the ESS is a more sensitive and clinically meaningful tool to evaluate the efficacy of modafinil in narcolepsy [20].
9. By measuring a clinically useful and well-used fatigue scale, the FISS-1, we are able to better gauge the relevance of the patient's sleepiness at a clinical level. Although we have added the FISS-2 to it, and cannot officially analyze it because there is no other standard for these questions, we have found that it is clinically useful appreciating the success of the interventions because the real world seldom contains a single individual diagnosis.

We now list our version of the MESS-R. At this point, any collaborations would be excellent for this and the PNI-FISS. We also welcome clinicians at this point using this in their practice provided they let us know at admin@pni.org that they're doing so.

Modified Epworth Sleepiness Scale (MESS-R) © PNI 2016

NAME: _____ DATE: _____

Please between 0 and 4 for the degree (how much?) it's been happening in the past week.

0 = you never or almost never doze when that's happening

1 = you have a slight chance of dozing

2 = you have a moderate chance of dozing

3 = you have a high chance of dozing

4 = you're almost always dozing when that's happening

Under normal circumstances, how likely are you to doze off or fall asleep in the following situations (in contrast to just feeling tired)? If you have not been in the situation in the past week, please imagine how it would affect you.	Never	Slight	Moderate	High	Always
1. Sitting and reading	0	1	2	3	4
2. Watching TV	0	1	2	3	4
3. Sitting, inactive in a public place (e.g. a theater or a meeting)	0	1	2	3	4
4. As a passenger in a car for an hour without a break	0	1	2	3	4
5. Lying down to rest in the afternoon when circumstances permit	0	1	2	3	4
6. Sitting and talking to someone	0	1	2	3	4
7. Sitting quietly after a lunch without alcohol	0	1	2	3	4
8. In a car, while stopped for a few minutes in traffic	0	1	2	3	4

Adapted from <http://www.stanford.edu/~dement/epworth.html> VMNeppe 2003, revised 2014

Please do not write here:

MESS R3 Score (1-3) = ; MESS-R4 score =

The Neppe Narcolepsy Questionnaire (NNQ): Part 4

The Neppe Narcolepsy Questionnaire (NNQ)

The Neppe Narcolepsy Questionnaire is a copyrighted screening questionnaire [25]. This developed out of necessity because as far as we're aware there is now equivalent.

It was needed in the running of the Pacific Neuropsychiatric Institute (PNI), as it would be for any Neuropsychiatric Institute.

Vernon Neppe authored an early version of this test in the 1982 while working in a Sleep-Wake Lab at the Division of Chronobiology, Cornell University, NY. Dr Neppe then adapted it

in the early 1990s. This has become critically important because there remains no test to screen for possible narcoleptic symptoms [23]. Recently, Dr Neppe updated the NNQ (2016) to include the latest criteria and ideas on narcolepsy and cataplexy. These were purely additions, with no subtractions so that our previous dataset remains.

We have used the Neppe Narcolepsy Questionnaire (NNQ) at the PNI in Seattle, WA [25] as a screen in every patient who exhibits any clues to narcolepsy, significant day time sleepiness on the modified PNI Modified Epworth Sleepiness Scale (MESS) or disproportionate sleepiness compared with fatigue on the modified PNI Fatigue Severity Scale Questionnaire (FISS).

So that we can manage the narcolepsy appropriately.

We can differentiate the non-narcolepsy primary dyssomnias with genetic positive HLA expression.

We can motivate use of wakefulness agents.

We can, in a structured fashion, speed up the evaluation as the patient records their symptoms which can be amplified.

We know what extra symptoms the patient has clinically.

We also are able to build a reservoir of experience and knowledge for the future.

We can also save significant expense because it almost always eliminates the need for polysomnography in narcolepsy (not sleep apnea), or for MSLT or CSF Orexin levels provided it is performed with genetic HLA testing (which is a simple blood test).

Table 4A: Why is the Neppe Narcolepsy Questionnaire used? [23,25].

The NNQ has been used regularly clinically (at the PNI) since 1992 for all patients in which the diagnosis of Narcolepsy or a narcoleptic syndrome is queried.

Patients complete this open answer questionnaire in Microsoft Word. The numbers of questions per item have changed over time including 2014 and 2016. The patients usually complete this in a short while (such as a hour0.

The NNQ covers the areas of:

- a) Nocturnal sleep (20 was 12 items),
- b) Day-time sleepiness (34 was 15 items plus subitems),
- c) Cataplexy (20 was 10 items),
- d) Sleep paralysis (13 was 9+ items),
- e) Special Tests (new only: subitems),
- f) Diplopia (18 was 5 items).

There are several extra items:

- a) Automatic Behavior (32 was 16 items with subitems),
- b) Perceptions (33 was 20+ items), Dreams (24 was 18+ items),
- c) Nocturnal Sleep Disorders (11 was 12 items) and
- d) Ego-Boundaries (23 was 12 items with subitems).

We cannot present comparative data because there is no other questionnaire. But it has proven extremely sensitive and specific in screening for symptoms of Narcolepsy based

on measures of diagnosis and also of clinical response to medication. (In twenty years we have not had patients where eventually we prescribed wakefulness agents and found the patients did not respond as expected. On the other hand we did not use these agents when not indicated, and managed with alternative medications. We can therefore argue that the use of the NNQ is proven.

In practice, the NNQ has always been combined with the HLA Narcolepsy screen and HLA-DS15 (DRB1*15), HLA-DQ6 (DQA1*0102/DQB1*0602). This has proven useful in supporting our expectations (clinical hypotheses) that the NNQ is valuable. As a point of interest, at the PNI, we might see more narcolepsy than anywhere else in WA state. Consequently, we have over the past two plus decades had the opportunity to see many variants. At times we see more patients because of loaded family histories. Our comments here are based on this experience.

The NNQ together with HLA have proven very useful. The utility is well documented on response to appropriate medications particularly wakefulness agents, such as Modafinil. Usage of these criteria differentiates two groups: A Narcolepsy diagnostic group and a Primary Dyssomnia (without Narcolepsy) syndrome.

Interestingly, a high proportion of these patients has temporolimbic instability and also require anticonvulsants.

I provide below the key aspects of the NNQ. Those wishing to use it in research or clinically should contact us at admin@pni.org.

Neppe Narcolepsy Questionnaire—4R (NNQ—4R) [25]

I. SLEEP HABITS:

1. Do you have difficulty sleeping?

If so, in what way?

Please describe approximate times when you sleep:

- a. During work days
 - b. During off days e.g. weekends.
2. How long does it take you to fall off to sleep?
 3. What time do you wake up in the morning?
 4. Do you wake during the night?
 - a. How often?
 5. How many hours a night are you sleeping?
 - a. During work days?
 - b. During off days e.g. weekends?
 6. Do you remember your dreams (on waking)?
 7. Do you sleep the same number of hours over weekends?
 8. Do your sleeping habits change?
 - a. In what way?

9. Do you feel tired when you wake up in the morning?

10. Do you wake up naturally or by other methods?

For example, alarm clocks?

11. Do you snore when you sleep?

12. Do you have any other experiences any time while you are sleeping at night? Describe.

13. Do you take any medications to go to sleep or any medicines at night?

14. Have you ever been given sleeping pills to take?

- a. Which ones?
- b. When?
- c. Frequency? Every night.
- d. Please go through each and indicate how they help or hinder you.

15. For how long do you sleep?

- a. Per night?
- b. Average?
- c. Shortest?
- d. Longest?

16. Have you ever been diagnosed with any of the following:

If yes, please answer when it was diagnosed and whether this is so?

- a) sleep apnea?
- b) narcolepsy?
- c) delayed sleep phase syndrome?
- d) advanced sleep phase syndrome?
- e) Sleep wake disorder associated with work?
- f) Sleep wake disorder associated with anything else?
- g) Seizures or epilepsy?
- h) Depression, anxiety or other mental related condition?

If yes to any of the above, please give details.

17. Do you use any kind of CPAP or other mask or nasal method while sleeping? If yes: Please amplify which one, what level, how frequently, and the success you've had?

18. How tall are you (in feet and inches or centimeters)?

19. What do you weigh? (in pounds or kg)

20. What was your maximum weight ever?

II. Daytime sleepiness (Uncontrolled DTS)

1. Do you fall asleep during the day?
2. How frequently is this on purpose?
3. How often is this against your will (you cannot control it)?
4. Is there a particular circumstances associated with your falling asleep? Describe.
5. How often during the day do you nap/sleep on the average?
 - a. Per 24-hour day?
 - b. Per night?
 - c. Average?
 - d. Shortest?
 - e. Longest?
6. How often during the day do you nap/sleep on the average?
7. How many times in the past month have you napped on average each day?
8. a. How many day-time naps do you average per day?
- b. What is the most?
- c. What is the least number?
9. Is this about the same over the past three months, or is it increasing or decreasing?
10. At what age did these episodes begin?

11. Was there ever a break period during this time when you didn't have these times of naps during the day?

Is there any reason you can think of?

12. Has there been other reasons like sleep apnea, recreational or other non-prescription drug use, prescription medications, or changes in your sleep-wake cycle during work? Please clarify and indicate if this made the condition worse or better.

13. When you nap during the day, do you have difficulty sleeping at night?

14. Can you control your going off to sleep during the day?

15. If you fall asleep during the day, do you feel refreshed thereafter?

a. How long do you feel refreshed for?

16. Can you return to sleep again or do you have difficulties getting to sleep once you have slept during the day?

17. Has this problem caused any difficulties in the past?

18. Have you ever fallen asleep while driving?

a. How often?

b. Have you had any serious accidents?

c. Any near misses?

d. Any car accidents where you might have fallen asleep or not been aware?

19. Have you ever fallen asleep while standing?

20. Have you ever fallen asleep while writing something?

21. Do you find that falling asleep relates to whether you are bored with the activity you are involved in?

22. Are you more likely to fall asleep doing something passively; like watching something or during periods of activity?

23. Are there any pointers for you that make you know that you are going to fall asleep during the day?

Describe.

24. Have you any warning of any kind, or do such episodes take you by surprise?

25. After napping how do you feel when you wake up?

26. Are you usually alert between naps?

27. Are you ever fully alert?

a. At all times other than napping?

b. Just after napping?

28. Do you sleep whenever you feel sleepy, or do you postpone or try to avoid sleep?

a. In what way?

29. At what age did your narcolepsy/uncontrollable sleepiness begin?

30. When was the last time you had this?\
31. Describe an example that is clearest to you or remembered best or the most severe one?
 32. a. Which medications recreational drugs or alcohol help and in what dose?
 - b. Which medications or recreational drugs or alcohol or other make these worse, and in what dose?
33. Does anyone in your family have episodes of uncontrollable sleeping during the day?

III. Cataplexy

1. Do your muscles sometimes feel weak or wobbly when you laugh or get angry?
2. Have you ever had episodes where parts of your body, for example, your face, start quivering, and you cannot control this? These are examples and please check any of these sudden symptoms that present:
 - a. Eyelids
 - b. Head drop
 - c. Facial sagging and twitching
 - d. Slurred speech
 - e. Jaw weakness
 - f. Head drop
 - g. Weakness in arms shoulders and hands
 - h. Buckling of knees
 - i. Have any doctors or professionals regarded this as sudden and transient loss or reduction of muscle tone?
3. When mild, do episodes involve legs, neck, face, eyelids, arms, or breathing, all or most of above? Please check which ones.
4. When severe, do episodes involve legs, neck, face, eyelids, arms, or breathing, all or most of above? Please check which ones.
5. Do you notice these features coming on in any particular way?
 6. a. When was the last time any of these occurred?
 - b. When was the first time any of these occurred?
 - c. How frequently do these events happen now?
 - d. At worst, how frequently did these events happen?
7. In your own words, please describe
 - a. a typical (cataplexy or equivalent) event like the ones above.
 - b. The most severe ones.
 - c. The most minor ones.
8. Which medications help and in what dose?
9. Which medications or recreational drugs or other make these worse, and in what dose?
10. Does anyone in your family have cataplexy episodes or anything like this? If so, whom?? Who? Please describe.
11. Have you ever found that while awake you've suddenly become paralyzed in terms of action or have sudden weakness in a part of your body or other kind of possible cataplexy episode.
 - a) Does this occur under any "particular circumstance"?
 - b) Have you ever had these symptoms while laughing? while crying, while surprised, while elated?
 - c. While having strong emotions?
 - d. While under stress?
 - e. While angry?
 - f. While surprised?
 - g. Doing nothing in particular?
 - h. Can you stop any of these symptoms?
 - i. as a child at any point even without triggers?
 - j. as an adult, at any point even without triggers?
12. How often does it happen? Almost everyday
 - a. When was the first time?
 - b. When was the last?
13. Have you ever found that while awake you've just fallen to the ground?
14. a. Have you ever felt drained of strength?
 - b. Do you ever feel lightheaded?
 - c. Have you ever lost consciousness with any of these episodes?
 - d. Do the symptoms (cataplexy) end in sleep?
 - e. If so: without dreams, with dreams, with day-dreams (almost awake)?
 - f. Have you ever found that while awake you've just fallen to the ground?
15. Are you more likely to have these symptoms (cataplexy) when you are sleepy?
16. a. Have you ever hurt yourself with these attacks?
 - b. Are you able to avoid injury because you've learnt to notice the feeling of these (cataplectic) attacks approaching?
 - c. Is the fall is usually slow and progressive over short

periods like seconds? Please amplify if needed.

17. How long do these attacks last? (seconds, minutes, hours)
 - a. Usually?
 - b. Shortest time?
 - c. Longest time?
18. Do you lose control of your eye movements during these episodes? Please explain if you do.
19. Some basics:
 - a. At what age did your symptoms begin?
 - b. When was the last time you had this?
 - c. Describe an example that is clearest to you or remembered best or the most severe one?
 - d. Does anyone in your family have episodes like this?
 - e. Which medications help and in what dose?
 - f. Which medications or recreational drugs or other make these worse, and in what dose?
 - g. Which medications or recreational drugs or alcohol help and in what dose?
 - h. Which medications or recreational drugs or alcohol other make these worse, and in what dose?
 - i. Does anyone in your family have such episodes or anything like this? If so, whom?? Who? Please describe.

IV. Sleep Paralysis SP

1. Do you sometimes while during sleep wake up to find yourself paralyzed, unable to move?
 - a) How often does this happen?
 - b) When was the last time?
 - c) Does this involve your whole body?
 - d) If so, which part?
 - e) How long does this last?
 - f) When did it first occur?
 - g) Do you experience this feeling as pleasant or unpleasant?

Indicate this proportion unpleasant to pleasant.
2. Do you find that during these experiences you have any particular thoughts?

Describe.
3. Do these experiences seem to lead on from any particular kind or dream?

Describe.

4. Are they associated with hallucinations or strange experiences?
5. At what age did your symptoms begin?
6. When was the last time you had this?
7. Describe an example that is clearest to you or remembered best or the most severe one?
8. Does anyone in your family have episodes like this?
9. Which medications help and in what dose?
10. Which medications or recreational drugs or other make these worse, and in what dose?
11. Which medications or recreational drugs or alcohol help and in what dose?
12. Which medications or recreational drugs or alcohol other make these worse, and in what dose?
13. Does anyone in your family have such episodes or anything like this? If so, whom?? Who? Please describe.

V. Special tests:

Please give the results of any of the tests you've had relating to sleep difficulties.

If you know the results, please record these. Also give dates, when available.

- a) Any kind of sleep recordings?
- b) Nocturnal polysomnogram-a measure of sleep during the night. (check: at home/ in a lab)?
- c) MSLT (multiple sleep latency test) (do you know how many times they measured this in one day)?
- d) Sleep apnea testing (check: at home/ in a lab)?
- e) Gene test for narcolepsy?
- f) Any other gene test?
- g) Spinal tap? (also called Lumbar puncture? CSF / cerebrospinal fluid/ Orexin test).

V. Diplopia

1. Do you ever see double?
 - a) How frequently does this occur?
 - b) Do you see double with both eyes or with one eye?
 - c) Does this occur on medication?
 - d) Does this occur off of medications?
 - e) At what age did this begin?
 - f) At what age did your symptoms begin?
 - g) When was the last time you had this?
 - h) Describe an example that is clearest to you or remembered best or the most severe one?

- i) Does anyone in your family have episodes like this?
- j) Which medications help and in what dose?
- k) Which medications or recreational drugs or other make these worse, and in what dose?
- l) Which medications or recreational drugs or alcohol help and in what dose?
- m) Which medications or recreational drugs or alcohol other make these worse, and in what dose?
- n) Does anyone in your family have such episodes or anything like this? If so, whom?? Who? Please describe.

VI. Automatic Behavior

1. Have you ever done something unusual and yet you were not aware of it until afterwards? (Elaborate: drove a car, had a strange conversation; walked a dog, or did something else)
 - a. How often?
2. Have you found that you have continued to drive your car and not been aware of it?
3. Have you ever been vaguely aware of carrying out an act?
 - a. In what way?
 - b. How often?
5. Have you ever performed any antisocial acts without your awareness?
6. Have you ever been violent without being aware of it?
7. Have you ever walked during sleep (= Experienced somnambulism)?
 - a. When was the first time?
 - b. When last?
8. Have you ever carried on writing doing something and not been aware of it?
9. Has your handwriting changed in any way during that period?
 - a. How?
10. What was the content of what you were writing?
11. Did that change in some way?
12. Then these episodes of behaving automatically occur?
 - a. How long did they last?
 - b. Average?
 - c. What is the longest they have ever lasted?
 - d. What is the shortest they have ever lasted?
- e. What time of day do they occur?
- f. Are they more common when sleepy?
13. Are these episodes of strange/unusual/'amnesic'/dreamlike behavior more likely to occur when you're very sleepy, such as when you've postponing or avoiding sleep?
14. Are these specific triggers or associated events?
15. What other features are associated?
16. Do you have any memories at all of them?
17. Are these memories at the beginning, the middle, or the end?
18. Do these memories come back?
19. Do you ever find that these lead from daydreams or lead into some kind of daydream?
20. Do you find that they occur more frequently when associated with particular symptoms?
21. Do they occur more frequently when associated with emotion?
 - a. With laughing?
 - b. With crying?
 - c. With shame?
22. Afterwards how you feel?
23. Do you have a headache?
 - a. If so, of what kind?
24. Do you feel sleepy or tired?
25. Do you feel confused in that you have difficulty being aware of where you are, or what day or date it is?
26. Have people ever told you that you were acting strangely?
27. What about nausea/vomiting?
28. dizziness?
29. Any pains?
30. Have you ever found yourself shaking uncontrollably during these other episodes?
 - a. If so, describe.
31. Has anyone in your family ever had symptoms of this kind?
 - a. At what age did these symptoms begin?
 - b. When was the last?
32. Describe an example that is clearest to you, or remember best.

VIII Perceptions No hypnopompic or hypnogogic phenomena.

1. Do you ever find that you have strange unusual or frightening experiences or voices, dreams or visions before going to sleep?
 - a. How often do you have them?
 - b. When was the last time?
 - c. At what age did they start?
2. Do you ever find that you have strange experiences during daytime?
 - a. While awake?
 - b. Or in association with any daytime naps?
3. Do you have strange experiences at any other time?
 - a. When?
4. Which of your senses have been involved; seeing, hearing, your sense of touch, temperature, your sense of self, your sense of taste, your sense of balance?
5. Do they involve any kind of pain?
6. Any kind of sensation within your body?
Limp, weak
7. Temperature change?
8. Do they relate to any form of stimulus or which you can experience or see, or is there nothing which has stimulated the experience?
9. Is what you perceive (experience) a distortion of something actually in the environment?
10. Are they pleasant or unpleasant?
 - a. What is the ratio?
11. Have others also experienced these with you?
12. How long do they last?
13. Does anything else sometimes happen while you're having these experiences?
 - a. And after?
14. Do they occur only in one perception, for example, seeing or hearing, or do they have many different kinds of sensations, for example, seeing and hearing together
 - a. What do they mean?
15. Do they have a 'knowledge' component?
16. Do they specifically refer to you?
17. Would you please describe what happens?
18. Is the experience mild or intense?

19. Do you experience these from outside?
20. Can you recognize who it is or what it is that you may be seeing or hearing?
21. Are there any other associated features?
22. Would you please describe when these occur?
23. Are they before sleep, after sleep, during the day, other times?
24. Are you frightened of objects, shadows, or sounds in your darken bedroom?
25. Are you intrigued by them?
26. Do you sleep in the dark?
 - a. If so, do these objects change in any way?
 - b. If not, do you perceive them as changed?
27. Do you at other times see or hear or in other ways experience a person or a thing which is a distortion of something which is present?
28. Have you ever found yourself outside of your body or feeling outside your body?
29. Have you ever experienced that your consciousness is outside yourself?
30. Have you ever seen yourself or felt yourself outside yourself?
31. Have you found that during these times when you hear or see things, you cannot move?
32. Have you ever had the experience that somehow you felt paralyzed during this (you couldn't move your body)?
 - a. What do you feel causes it? I'm focused on what's outside of my not my body
 - b. Have these occurred during periods of high emotion?
33. Any family history?

IX Dreams

For all the following experiences, indicate whether they occur during daytime

naps or during the night, so that they are in fact two series of answers:

1. Do you dream? (remember dreaming)
2. Do you dream in:
 - a. color
 - b. black and white?
3. Are there any particular colors you find yourself dreaming in?
4. Have you ever had the impression that you know you

are dreaming but you feel you are awake even though you are asleep and dreaming?

5. Have you ever been aware of yourself dreaming while you were dreaming?

- a. When last?
 - b. How often?
 - c. When was the first time?
 - d. Are your dreams very clear?
 - e. Are your dreams vivid or lifelike?
 - f. More so than before?
6. Is there any special quality to any of your dreams?
7. How frequently do you recall your dreams?
- a. Immediately upon on waking?
 - b. At lunch-time the same day?
 - c. The next day?
8. Do you dream during the daytime?
9. Do you dream about any particular events?

10. Do you feel that most of your dreams relate to the events of the previous day?

11. Have you ever had dreams where you felt you've had a special knowledge about something or been able to predict something?

12. How long do you feel your dreams last?
13. Do you ever have the same dream repetitively?

14. Do you ever find that if you wake up, you can re-continue your dream where you left off?

- a. In what detail are you able to recall your dreams?

15. Do you ever have dreams where you feel you are paralyzed?

- a. When?
16. Do you ever have dreams where you are very active?
17. Don't have any weight, you feel weightless?

18. Do you have strange kinds of dreams during the day where you would not have felt you were sleeping, but you seem you must have?

19. Do you daydream?

20. Have you ever dreamed about something and you later learned that what you dreamed really happened?

21. Have you ever had a rather clear and specific dream which matched in detail an event which occurred before, during or after your dream and which you did not know about and did not expect at the time of this dream?

a. How many times have you had this dream?

b. Please describe separate instances.

22. Do you believe your dreams can foretell the future?

a. Or allow special knowledge for you?

23. Have you ever had a dream involving someone and later learnt that that person had the same dream as you did at the same time?

a. If so, describe separate instances.

24. When you awake from dreaming, how long does it take to reorient yourself?

IX. Sleep Disorders of Any Kind During the Night:

Daytime Sleepiness; Hallucinations of Any Kind; Illusions of Any Kind; Sleep Paralysis; Cataplexy; Diplopia; Strange Dream Experiences; Automatic (For all of these questions please describe at what age each one of these features began).

1. Are there any members of your family who have any of these experiences?

a. Please list:

2. Which medications have you been taking?

3. What is the present frequency of each symptom?

4. What was the greatest frequency when they were worst?

5. What effect do your medications have on each symptom?

6. Have you ever abused any non-prescribed drugs?

7. What medications have you been on for your problem?

8. Which medications do you find work best?

9. Have you ever had a sleep test that the doctors called an MSLT?

10. Have you ever had a sleep recording at night?

11. Have you any other sleep related conditions or behaviors or sleep apnea

X. Ego-Boundaries

The following questions have subsections and may seem unusual. You need not fear answering positively to them.

1. Have you ever had "psychic" or paranormal experiences?

a. How many?

b. Were these of everyday things or of major events?

c. Were these proven right?

d. What did they mean?

2. How psychic are you?

a. Why you specifically?

3. Have you ever had telepathic or ESP experiences? (i.e.,

the strong feeling” or knowledge that something unexpected was happening or had happened or would happen.)

- a. Please describe.
 - b. Were you right?
 - c. What did it mean?
 - d. Why to you?
4. Have you ever healed someone?
5. Do you have special healing powers?
- a. Please describe.
 - b. What success have you had?
 - c. What does this mean?
6. Have you ever:
- a. made something move from afar?
 - b. bent something with your mind?
 - c. stopped a watch?
 - d. found your watch cannot run for no apparent reason?
7. Describe.
- a. What does this mean to you?
 - b. Why can you do it?
8. Have you ever had a memory of a previous existence? (i.e., as if you’ve lived before or had another life)
- a. Please describe.
 - b. Have you ever recognized yourself as someone important or famous?
 - c. How is this possible?
 - d. Do you think it is likely?
9. Have you ever been in a trance?
10. Have you ever found somebody else controlling your thoughts or your thinking?
- a. Or your writing?
 - b. Or your speech?
 - c. Describe.
 - d. Who was this?
 - e. What does it mean?
 - f. Why does it happen to you?
11. Have you ever had the impression (or awareness or saw or heard or smelt or sensed) that someone or something not physically or really present was there?
12. Or have you felt colors or lights or an aura around someone or part of them?

Describe.

- a. Were you awake?
 - b. What does it mean?
 - c. Why you?
13. Does someone or something, known or unknown to you sometimes control your thoughts or your thinking?
- a. What about your feelings - your emotions?
 - b. Is someone or something from outside controlling your thoughts?
14. Can you control your actions fully at all times?
- a. Or does someone or something influence them by some means?
 - b. What about parts of your body?
15. Do you find that an outside force does things using you as a vehicle?
- a. Or thinks some things?
 - b. Or feels (experiences an emotion) in a particular way?
16. Does an outside force or influence sometimes do things which actually look like it’s being done by you?
- a. Describe.
 - b. Why?
 - c. What does it mean?
17. Can others read your thoughts?
- a. How?
 - b. Why do they do it?
 - c. Is it only your thoughts that can be read?
 - d. Do they extract (take or steal) your thoughts (out of your head)?
18. Can you communicate by telepathy?
19. Can you read their thoughts?
- a. How?
 - b. Describe?
20. Does everyone have these powers?
- a. Why you?
21. Do you sometimes hear your own thoughts?
- a. Where do you hear them?
 - b. Describe.
22. Do you sometimes feel alien?
- a. Describe.

23. a. Do your thoughts sometimes stop?
 - b. Or you suddenly experience nothing?
 - c. Or do your thoughts sometimes feel unclear?
 - d. Like they are falling over each other?
 - e. Or they cannot connect?
 - f. Or they are like wool?

The Genetics of Narcolepsy: Part 5

No gold standard currently exists for the diagnosis of narcolepsy. Conventional diagnostic criteria have often been unwieldy, requiring low CSF orexin (same as “hypocretin”), or 2 positive SORMPS out of 4 or 5 or 6 under strict MSLT conditions. The criteria are often arbitrary and varies. Yet, in research, defined criteria for case selection are needed to compare the results of different studies [3]. Even more so real interpretation is required clinically.

Most importantly, it seems that based on the data available, we can ensure a diagnosis of narcolepsy that is appropriate in the high 90% range. This can be easily done by clinically applying careful evaluations and structured questionnaires. This allows making sure the patient’s day-time sleepiness conforms to the narcolepsy label, that the patient has cataplexy features which makes the diagnosis more specific, and that the patient expresses HLA DQB1*0602. If this happens, and this triad of features based on research occurs in some 85% of cases, we can be reasonably certain that the patient will also have a CSF hypocretin/ orexin deficiency. We will therefore know the cause biologically is due to the disease state of narcolepsy. This data is not new, but has been known since 2002 [3].

MSLT may be valuable in the small proportion of patients who fail in this assessment: this will include either or both of narcolepsy without cataplexy, or those who do not express HLA DQB1*0602, but they might even include those who on CSF do not have a hypocretin state. I humbly submit that at this point, these exceptions are at best unproven entities and that biologically they might not be narcoleptic and may reflect more than one condition or subtype. Yet, we don’t have studies, at this point, proving different conditions or subtypes.

Let’s look at the information available on the HLA gene. We know that:

- i) Even as long ago as 2002, new research diagnostic criteria for narcolepsy were based on HLA typing. These possessed high interrater reliability and appeared valid descriptors of the syndrome. These results may be useful in providing consistent criteria to compare different research studies [3]. Why?
- ii) The key, most common gene involved in narcolepsy is HLA DQB1*0602: depending on the study, about seven eighths [39] or even 12/13 [1] of cataplexy patients, but only 33% of those with narcolepsy features without cataplexy, express the gene [3]. The question is: Are these figures of the those who do not express

the correct HLA gene reflecting poor clinical diagnoses and not representing narcolepsy, or are they accurate? Clinically, this is unanswered completely, but they likely accurately reflect different diagnoses based on rankings of narcolepsy diagnoses [3]. Why?

- iii) The HLA-DQB1*02 frequency is also increased in the population with hypersomnia when compared with the control population ($p = 0.004$) But enough with hypersomnia without narcolepsy are positive that we need other tests. This means effectively that the *0602 expression reveals potentially more than narcolepsy and therefore that it may encompass any dyssomnia. My own impression is that if one is very careful in a neuropsychiatric population: We have found that even those “controls” who express *0602 have, in every case, expressed some kind of sleep disturbance. A 34% figure of “controls” from this study [40]. is the highest in the literature [3] with 16% being a more common estimate [40], and there may even be only 10% or less so-called false positives depending on the population [23]. I argue that the difference is an epidemiological one, depending on how skewed and symptomatic the population is. But, I humbly submit that we could be talking about the far more common “primary narcolepsy”, with the usual gene expression, and if tested this would imply low orexin and likely auto-immune components, and “symptomatic narcolepsy”, with secondary brain damage at the hypothalamic RAS level. This can manifest in many ways: I’ve even seen a case mobilized by cysticercosis.
- iv) The evidence is so strong that if DQB1*06:02 is positive, subjects are at a 251-fold increase in risk for narcolepsy [41]! An overwhelming portion of genetic risk for narcolepsy with cataplexy is found at this DQB1 locus [41], but importantly other loci such as DQA may also be relevant and therefore tests should be for both loci, particularly as expression at both loci might show higher penetrance of symptoms.
- v) Without HLA-DQB1*02 expression, it is very unlikely that narcolepsy exists [40]. My impression is that, yes, narcoleptic syndrome could exist but this is due to possible damage to the Orexin or hypothalamo-reticulo-activating system dysfunction due to trauma, tumor or infection. So the absence of genes does not then exclude narcolepsy, but the clinical situation must provide much stronger evidence.
- vi) We generally need not demonstrate low CSF hypocretin-1 levels. This is because we know, based on other research, that low hypocretin will likely be present in about 85% of cases with DQB1*06:02 expression and cataplexy. However, if the patient does not have cataplexy, only about one fifth of such patients will have low CSF hypocretin-1 levels: This is a curiosity, because cataplexy sometimes takes some years to develop after the narcolepsy day time sleepiness. This might mean that the low CSF hypocretin-1 levels are not primary but secondary to progression of the illness.

- vii) However, rare cases (about one in sixty) are DQB1*06:02 negative with low CSF hypocretin-1. These occur equally with or without cataplexy: Therefore, even hypocretin does not correlate fully. There are rare HLA negative subjects with severe cataplexy, but often without clear triggers [39]. This might suggest that another gene could be involved, so we need to look further here.
- viii) Although HLA-DQB1*06:02 is the strongest predisposing genetic factor for narcolepsy, the effect of this gene must therefore be considered alongside that of others, and that turns out to be its polymorphic partner, DQA1 [39].
- ix) HLA-DQB1*06:02 allele with narcolepsy and cataplexy is clearly a major predictor of cataplexy in narcoleptic patients. We argue that the literatures' supports it could be used as an additional diagnostic marker alongside Hypocretin [42]. This may seem obvious but bears mention because the literature seldom points this out.
- x) The genetic basis for narcolepsy may also be linked increased susceptibility to infectious factors or an immune cytotoxic mechanism in narcolepsy, potentially targeting hypocretin neurons: this may be linked not only with DQB1 gene but DQA [43].
- xi) A secondary HLA-DP association may be present in rare cases representing particularly difficult diagnostic challenges: The rare subtype DPB1*0901, and homologous DPB1*10:01 subtype [39]. However, it does point out that occasionally there are other ways of narcolepsy expression.
- xii) The HLA-DQB1*06:02 involves a functional HLA-DQ molecule consists of a DQ alpha and a DQ beta chain. The HLA-DQB1*06:02 (DQ beta) has a strong preference for binding to HLA-DQA1*01:02 (DQ alpha), and together they form the functional DQ0602 dimer [44].
- xiii) In individuals homozygous for HLA-DQB1*06:02-DQA1*01:02, a dosage effect would be expected if the HLA-DQ0602 dimer itself is directly involved in the etiology. This does occur. An increased expression of the HLA-DQ0602 dimer is expected in individuals homozygous for HLA-DQB1*06:02-DQA1*01:02, but is also hypothesized in individuals heterozygous for HLA-DQB1*06:02 and homozygous for HLA-DQA1*01:02. A Dutch study showed importantly, a significantly higher prevalence of homozygosity for DQA1*01:02 was found in HLA-DQB1*06:02 heterozygous patients compared to controls (O.R. 2.37, $p < 0.001$). The latter finding clearly supports a direct role of the HLA-DQ molecule in the development of disease. 44 It also suggests that all studies should include DQA1*01:02 as well as DQB1*06:02. This is supported by other genetic studies [45].
- xiv) HLA genes likely function under an incomplete penetrance model, with possible influences from environmental factors or other genes different to HLA genes [46]. This may explain why patients from the same family, and with the same main gene expressions like 0602, still vary markedly in symptoms. 46 At least some of these patients have markedly loaded family histories and autosomal dominant inheritance is likely [47-49].
- xv) Few sleep disorders have an established genetic basis including four rare diseases that may result from a single gene mutation: fatal familial insomnia, familial advanced sleep-phase syndrome, chronic primary insomnia, and narcolepsy with cataplexy. However, most sleep disorders are complex in terms of their genetic susceptibility together with the variable expressivity of the phenotype even within a same family [50]. The extent of penetrance of genes is pertinent here.
- xvi) Finally, reanalyzing the genes, it may be even more complex. There may be protective genes based on Chinese work. HLA-DPA1(*)01:03-DPB1(*)04:02 (DP0402; [51]. They also found an independent predisposing effect of DQB1*03:01 predisposes via a currently unknown mechanism which might explain the few that are not due to the 06:02 gene. They also reported strong protective effects of HLA-DPA1(*)01:03-DPB1(*)04:02 (DP0402 and HLA-DPA1(*)01:03-DPB1(*)04:01 (DP0401 and predisposing effects of HLA-DPB1(*)05:01 [52]. It is clear that both DQA1 and DQB1 influence narcolepsy risk [51,52].
- xvii) Moreover, genome wide association studies have subsequently been able to prove that autoimmune mechanisms are responsible for the manifestation of narcolepsy with the HLA association being the most important for susceptibility and protection [10].
- xviii) Unlike the case of canine narcolepsy, where mutations in the hypocretin (orexin) neuropeptide precursor (HCRT) receptor have been found, it has been argued that Orexin deficiency is the cause of human narcolepsy [31,53]. The recent advances in the elucidation of the genetics of canine narcolepsy and the pathophysiologic role of hypocretin, in animals and humans, enhances current diagnostic capability and will ultimately provide better treatment modalities in the future [27], as well as clarify etiological and diagnostic issues.
- xix) Data also suggests that narcolepsy may be the result of an autoimmune reaction triggered by H1N1 vaccination in susceptible individuals [54].
- xx) Given these differences, and the above data, it might support the possibility of HLA genes and associated receptor expressions being fundamental.
- xxi) Moreover, Mignot's analysis could explain increased disease heterogeneity in a non-cataplexy group and a direct effect of the HLA DQB1*0602 genotype on the clinical expression of narcolepsy supports this [55].
- xxii) Based on this data, it appears that the gene expression

may be even more basic than the low orexin / hypocretin levels which may be secondary: This is a new Neppe hypothesis using this data. Effectively, the current idea has been that hypocretin deficiency causes the narcolepsy. I propose that based on the HLA data the cause is higher up the stream, and orexin deficiency is a consequence, albeit an early consequence downstream, but not a cause. A way to test this is to find patients with HLA DQB1 * 06:02 gene expression, with any early symptoms of narcolepsy, but which has normal orexin, and then with progression, later deficient orexin.

Nuggets

- a. Further characterization of the HLA genes could potentially enhance differential diagnosis among those expressing different kinds of excessive daytime sleepiness and this may correspond with diverse entities with different biological mechanisms [40]. But this is too specialized. Let's just remember the rules, not the exceptions.
- b. We must test both for the DQA and DQB genes. A recent and changed but common habit, certainly in our geographical area, is labs just doing the HLA-DQB1*06:02. This misses the other genes involved and may provide insufficient data for clinical assessment and later comparative clinical research, too. At minimum, DQA1*01:02 should be performed.
- c. In my experience over the past 20 years, in my neuropsychiatric populations, every patient expressing the gene has on careful analysis had some kind of dyssomnia: This is not a "normal" control population by any means.

Management of narcolepsy: Part 6

Two conditions are treated in narcolepsy.

The first is day-time sleepiness.

Current treatment recommendations suggest that these wakefulness drugs (also called wakefulness-promoting agent or eugeroics) should be used as a first-line treatment ahead of conventional stimulants such as methylphenidate or sodium oxybate [56].

The advent of modafinil (Provigil in USA) and armodafinil (Nuvigil in USA) (it's daughter effectively with a longer half-life allowing daily not BID management at times) has revolutionized management of narcolepsy [57]. It is indicated for narcolepsy, shift work sleep disorder, and excessive daytime sleepiness associated with obstructive sleep apnea [58]. It is not indicated in cataplexy.

Modafinil and Armodafinil is a schedule IV controlled substance with restricted availability and usage in the USA, though in many countries it is a prescription drug, but not further controlled.

Although the mechanism of action of modafinil and armodafinil was initially unknown, we do know it does act as a selective, relatively weak, atypical dopamine reuptake

inhibitor, possibly as a dopamine transporter reuptake inhibitor [57].

Modafinil produces wakefulness reportedly without the need for compensatory sleep, and shows a relatively low, if any [59], potential for abuse, through mechanisms e.g. cholinergic may be pertinent.

What is useful in follow up is the ability of sleep-stage sequencing of sleep-onset rapid eye movement periods in the multiple sleep latency test to predict treatment response, in narcolepsy, with cataplexy or without, applying clinical and polysomnographic criteria. This can be used in monitoring response to medications [56]. However, as indicated, the Epworth Sleepiness Scale appears more effective when using modafinil in narcolepsy [20] and also in obstructive sleep apnea [36].

The second medication approach is in the management of the Cataplexy.

Sodium oxybate and gamma-hydroxybutyrate has been found to be effective at reducing the number of cataplexy episodes. Sodium oxybate is generally safe and typically the recommended treatment for some clinicians as the most effective agent.

Sodium oxybate (USAN) (Xyrem from Jazz Pharma USA) is designated as an orphan drug, a pharmaceutical drug developed specifically to treat an orphan disease, cataplexy and narcolepsy. It is FDA approved for the treatment of excessive daytime sleepiness (EDS) associated with narcolepsy, and for the treatment of cataplexy associated with narcolepsy. and under the name Alcover, it is used in Italy for treatment of alcohol withdrawal and dependence. Therefore, it's the only drug marketed for narcolepsy EDS and cataplexy. It is generally well tolerated by most patients. The drug has been safely used by patients with narcolepsy since 2002, with surprising low rates of abuse, dependence, and withdrawal, and very rare sexual assault cases.

The active metabolite of sodium oxybate, gamma-hydroxybutyric acid, acts as an agonist at the GABA-B receptor complex and the GHB receptor. This likely contributes to some part of sodium oxybate's therapeutic effects.

However, it is a central nervous system depressant and must be taken exactly as prescribed. My biggest problem with oxybate is a practical one: patients must take it at night and wake in the night to take the second dose. A lesser irritation is simply that and patients should not eat for two hours before bedtime.

Instead, my own preference is for tricyclic antidepressants. I have been using nortriptyline but others use imipramine, clomipramine or protriptyline; venlafaxine is possible, although it can be argued that the benefit is not as good. I have seen recommendations pertaining to SSRIs, but I have no proof all are effective, and if so that the effect will be maintained for prolonged periods. Because tricyclics have been available for up to 60 years, we know they do not appear to lose efficacy certainly in depression.

These compounds work to manage both cataplexy and the REM sleep-onset symptoms of sleep paralysis and hypnagogic hallucinations.

Non-pharmacological management

Non-pharmacological management of narcolepsy is important: Patients should maintain a strict regular wake-sleep schedule and good sleep hygiene. They should benefit from voluntary afternoon naps and a program of regular exercise [33]. Importantly, many cataplectics try to avoid highly emotionally charged situations such as laughter.

Treatment is highly individualized, depending on the severity of daytime sleepiness, cataplexy and sleep disruption.

Nuggets

Patients with narcolepsy should respond to modafinil or armodafinil. Dosage varies greatly.

Patients with cataplexy need tricyclic antidepressants like nortriptyline in low to medium doses.

Patients with hypnagogic hallucinatory phenomena sometimes respond to small doses of atypical neuroleptics like aripiprazole 2mg to 5mg daily (but this is an out of label use).

Mechanisms of narcolepsy: Part 7

The current postulated cause of narcolepsy is due to an autoimmune destruction of the neurotransmitter hypocretin, which regulates arousal and wakefulness. This leads to a low level of CSF hypocretin. We know further that damage to orexin-secreting neurons in the hypothalamus can lead to inhibition of motor neurons, thus lowering muscle tone.

Cataplexy

The neurological process behind the lesion of narcolepsy is the impairment of descending pathways controlling the normal inhibition of muscle tone, consequently, cataplexy results with muscle atonia [60].

This loss of tonus is caused by massive inhibition of motor neurons in the spinal cord. When this happens during waking, the victims of cataplectic attacks lose control of their muscles.

However, even though it is not apparent, muscle tone paralysis occurs at inappropriate times, but, nevertheless, the patient still continues to breathe and is able to control eye movements [61]. This is postulated and likely to be because this phenomenon is linked with Rapid Eye Movement (REM) sleep.

The hypothalamus region of the brain regulates basic functions of hormone release, emotional expression and sleep. The absence of neuro-excitatory properties of the hypothalamic hypocretin-peptidergic system [33] appears linked with the neurochemical hypocretin (Orexin), which is regulated by the hypothalamus. Hypocretin is significantly reduced in almost all patients with the symptoms of cataplexy, and is the primary chemical important in regulating sleep and states of arousal. Hypocretin deficiency is further associated

with decreased levels of histamine and epinephrine, which are chemicals important in promoting wakefulness, arousal and alertness.

Substitution of the deficient neuropeptides by hypocretin agonists [62] is a possible causal treatment strategy if this is, indeed, the etiology, or even if this is an early result of cataplexy and EDS.

The reticular activating system

The reticular activating system involves up and down stimulations [63].

The muscular paralysis can be perceived as the reverse effect of the sleepiness. The Reticular Activating System (RAS) goes to sleep in the other direction at an inappropriate time—so to say when RAS phenomena occur upwards. When this upward component happens during waking, we argue that the patient falls asleep and the kind of firing results in rapid-eye-movement sleep almost immediately with or without stage 1 sleep.

When the downward component happens during waking, the patient with a cataplectic attack loses control of some of their muscles [32,63]. This loss of tone is caused by massive or limited inhibition of motor neurons in the spinal cord.

Hypocretin deficiency

Hypocretin levels can be measured using cerebrospinal fluid (CSF) hypocretin-1 immunoreactivity values: Deficiency is currently regarded as a level of less than or equal to one-third of values obtained in healthy subjects tested using the same assay, and this usually works out to less than or equal to 110 pg/mL. Nevertheless, some argue that the optimal cutoff of CSF hypocretin-1 for narcolepsy without cataplexy diagnosis should be as high as 200 pg/ml rather than 110 pg/ml. [64]. A limitation is that CSF levels of hypocretin-1 should not be assessed in the context of acute brain injury, inflammation, or infection.

Patients with narcolepsy possess a reduced number of hypocretin-producing neurons in the hypothalamus and accordingly the hypocretin level in the cerebrospinal fluid is low [10].

Anatomically, hypocretinerigic axons make asymmetric synapses with neurons within the locus ceruleus, ventral tegmental area, dorsal raphe nucleus and laterodorsal tegmental nucleus that target the medial frontal cortex. Hypocretins could facilitate wakefulness and cortical activation, therefore, by activation of those neurons with cortical projections in these four reticular nuclei [65].

The neuropeptide hypocretin (orexin) has functions, such as the regulation of the sleep-wake cycle, the autonomous nerve system, motor system and metabolic processes [10].

Imaging studies have revealed neurodegenerative changes, making a multifactorial etiopathogenesis probable. The frequent occurrence of metabolic disorders has not yet been clarified. 10 And certainly puzzling are those few cases with

normal hypocretin levels in the CSF. Does this imply a second process such as resistance to the receptor, or another cause, or as indicated, that the hypocretin deficiency certainly is an important result, but minimally downstream and not the primary etiology.

How do low hypocretin patients compare with normal hypocretin measures on NPSG and MSLT? These patients have far more frequent short rapid-eye movement (REM) sleep latency during polysomnography, as well as shorter sleep latencies and more sleep-onset REM periods during the Multiple Sleep Latency Test (MSLT) [64].

In essence, current thinking is that measuring CSF hypocretin-1 is a definitive diagnostic test, provided that it is interpreted within the clinical context [66]. It has limited use when the MSLT is difficult to interpret as in subjects who are already treated with psychoactive drugs or with other concurrent sleep disorders [66].

Nugget

The question is “how far down in the narcolepsy cycle is the orexin data”? A small proportion of cataplectics have normal orexin levels yet express abnormal DQB genes [67]. Could it be that the damage is reflecting hypothalamic abnormalities and, as seen in the HLA discussion, based on this data, it appears that the gene expression may be even more basic than the slightly downstream low orexin / hypocretin levels, which then may be secondary? In this paper, I have suggested this as a feasible and possible new hypothesis, because the HLA data as a whole supports this line of reasoning.

Multiple Sleep Latency Test (MSLT): Part 8

The Multiple Sleep Latency Test (MSLT) test has become a routinely recommended evaluation to be performed in Sleep Labs for the diagnosis of narcolepsy [68].

Without doubt, the test has some strong virtues in assisting difficult diagnoses and in monitoring changes after treatment, but that must be put in a perspective.

In essence, there are some major difficulties, as well, about performing the MSLT:

- a. first, the test works out as very expensive;
- b. secondly, it is a specialized test where ordinary clinicians in psychiatry, neurology or family practice are effectively bypassed;
- c. thirdly, it does not yield an adequately high positive rate;
- d. fourthly, a good proportion of those without narcolepsy have false positives;
- e. fifthly, in my opinion, the MSLT is not necessary in most instances because the diagnosis is clear without it but with a good evaluation; and amplifying this,
- f. sixthly, and possibly most importantly, we argue that

- g. simply good clinical information (based on structured historical responses such as the Modified Epworth Sleep Scale and the PNI Fatigue Severity Scale as an initial screen, followed by the Neppe Narcolepsy Questionnaire, all combined with an experienced clinician in the area)
- h. combined with HLA testing of both the DQ-B and DQ-A series, and
- i. monitoring pharmacological response is usually adequate.
- j. Only then, if there are questions, the MSLT should be performed, with or without CSF Orexin (Hypocretin) levels.

The problem might be more complex. MSLT is expensive, and when narcolepsy is diagnosed or suspected, but MSLT does not prove the condition, then often the insurance companies will not approve the costs of wakefulness drugs treatment, which on an extended lifetime basis, using today's prices, is extraordinarily expensive. If this happens, patients may not be able to afford their treatment and they might deteriorate, be unable to work, have disruptive family lives, and suffer a great deal and compromise their families. And therefore, if they have a narcolepsy diagnosis, and are already responding to modafinil or armodafinil, this creates a major risk for them, as their medical record might say that they do not have a positive MSLT. That is potentially tragic.

In other words, I argue that there must another acceptable route for the medical insurances in the USA, certainly, to approve what the treating physicians regard as appropriate diagnoses of narcolepsy with or without cataplexy, when these patients have been evaluated even without MSLT. That acceptable route should be clinical and scoring data e.g. Epworth, plus NNQ or other historical standard protocol, plus expression of HLA-DQB-0602.

The problem may be more insidious. Why not just get an MSLT even though the diagnosis is relatively certain, including marked family histories? The difficulty is the “normal” MSLT result because at that point the patient who merits treatment on the basis of the previous narcolepsy evaluation (as listed in the sixth point above) may be denied costly pharmacological interventions by the medical insurances, and may not be able to afford the medications. This can be catastrophic for their future. Sadly, we personally have seen this happening on a number of occasions, and see as this as very tragic: Patients have literally lost their livelihood because they could not work and the insurances would not approve what for them are life-saving medications.

Additionally, as Mayer points out, the MSLT is a poor gold standard [69].

Effectively, the ICSD-4 is, in any event, easily applicable in cases with typical cataplexy and narcolepsy where with the MSLT, further evaluations are almost always positive and may thus not always be needed [1]. The main conundrum lies with patients without cataplexy who are difficult to classify

[1]. These patients' results might demonstrate difficulties in interpreting the MSLT, particularly in the presence of sleep apnea or reduced sleep.

Let's briefly examine the utility of the Multiple Sleep Latency Test (MSLT).

The most common criteria used is a multiple sleep latency test involves examining for Sleep Onset Rapid Eye Movement periods (SOREMPs). The MSLT test consists of four or five or even six 20-minute nap opportunities set two hours apart. The patient is monitored to measure the time elapsed from the start of a daytime nap period to the first signs of sleep and sleep latency. For a SOREMP to be positive, it should showing a mean sleep latency less than or equal to 8 minutes. For an MSLT there should be two or more SOREMPs. Technically, therefore, there should be two episodes of almost REM onset sleep for diagnosis or close to that, with up to a few minutes of a little stage 1 sleep beforehand, being acceptable. This criterion might be too stringent and diminish yield, but if there was only one SOREMP that might be too easy. This view is supported: Dauvilliers argues that the MSLT criteria indeed are too stringent certainly in the older population [8].

An alternative that counts for one SOREMP in the American Academy of Sleep Medicine (AASM) classification, is a SOREMP (this time showing latency to rapid eye movement (REM) sleep of less than or equal to 15 minutes of sleep onset) on the preceding nocturnal polysomnogram (PSG) and this may replace one of the SOREMPs on the MSLT. Nocturnal polysomnography (NPSG) sometimes precedes they multiple sleep latency testing (MSLT).

The NPSG of a narcoleptic patient may be totally normal, or demonstrate the patient has a short nocturnal REM sleep latency (suggesting narcolepsy), or the patient may exhibit separate unexplained arousals or periodic leg movements [33].

Based on sleep wave measurements, the diagnosis of narcolepsy is therefore supported by the presence of two or more sleep onset REM periods (SOREMPs) in the MSLT, or sleep onset REM periods (SOREMPs). Let's re-examine this.

Sansa et al examined the distribution of SOREMPs throughout the MSLT in narcolepsy with and without cataplexy. They applied the common five-nap test in MSLT, which requires at least two such tests to be positive. On average, about one fifth of these nap tests showed SORMPS and the fourth test in that sample was about a sixth. Shortening the MSLT to three or four naps decreased the capability of the test even more to support the diagnosis of narcolepsy [6].

Sleep laboratory testing should be performed according to standard techniques, and results should be carefully interpreted in the context of the patient's clinical history in the presence of EDS. At least 1 week of Actigraphy assessment with a sleep log is strongly recommended prior to MSLT to determine factors that may bias results (e.g., insufficient sleep,

shift work, or other circadian rhythm disorder). These reflect stringencies in the MSLT procedure (as behooves any logical test), for example, the patient should not have slept less than 6 hours prior to MSLT, and the issues of medication will vary: for example, on what one is monitoring e.g. response to treatment is one parameter.

Hypersomnolence and/or MSLT findings should not be better explained by other causes such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal.

On the other hand, in another study, patients with definitive orexin findings, and proven narcolepsy with cataplexy, have much higher sensitivity of 96% with specificity of 74%, whereas two SOREMPs had a sensitivity of 75%, with a specificity of 95% for a pathological REM sleep propensity at MSLT. In this population, which likely does not require clinical selection at all because it is definitive, the multiple spontaneous SOREMPs during daytime clearly identified patients with narcolepsy [68].

MSLT can also prognosticate: The presence of this specific sleep-stage sequence in all sleep-onset rapid eye movement periods was associated with worse treatment response and aid the prediction of treatment response in narcoleptics and provide a useful prognostic tool in clinical practice [56]. However, we could logically hypothesize that simply monitoring severity of clinical episodes e.g. by Epworth score, or the presence of HLA genes both DQA and DQB [46], or pharmacological response, might provide an even more adequate monitoring test, as well, but the research has not adequately explored that.

These tests MSLT, Orexin, HLA are controversial in their interpretation: As I regard the literature currently including much of the research, routine MSLT is not required to prove diagnoses of narcolepsy when clinical (including structured histories) and HLA confirmation confirms the diagnosis of both narcolepsy and cataplexy. Technically, classifications have varied with what has been called Narcolepsy Type 1 involving both excessive daytime sleepiness (EDS) and cataplexy as core features, and Narcolepsy Type 2 requiring the excessive daytime sleepiness as the essential feature but where cataplexy is absent. These criteria seem reasonable except one can say "Narcolepsy with Cataplexy instead of Type 1, and "without Cataplexy" instead of Type 2. The problem comes when some classifications add additions such as MSLT and / or CST orexin as mandatory criteria: Those additions exclude most conditions from being either Type 1 or Type 2 because those tests have not been done. Additionally, if we examine the literature carefully, it is astonishing that HLA testing for narcolepsy has just been excluded in almost every list of fundamental criteria.

Without cataplexy, MSLT for narcolepsy may be useful but should not be overvalued because it is not a gold standard, as in the real world there are often complicating features, such as additional obstructive sleep apnea.

Perspective on narcolepsy and cataplexy: Part 9

This final section is best illustrated with tables. First, I describe, again, the classical narcolepsy quartet where day-

time sleepiness and cataplexy are far more important clinically than the other symptoms which may be non-specific and so not diagnostic and are difficult to conceptualize.

Day-time sleepiness: This involves uncontrolled sleepiness. Very commonly has a history of falling asleep while driving. After a 20 minute nap with or without remembered dreams, there is an episode of several hours of refractoriness during which the patient is very refreshed.

Cataplexy: This loss of tone often occurs with high emotion. It can involve small groups of muscles and sometimes involves dropping objects, or the knees buckling. It can manifest with any group, but in our experience may be consistent for that individual. Cataplexy is very common and leads to a classification of Narcolepsy with cataplexy and Narcolepsy without cataplexy.

Sleep paralysis: This is likely associated with the hypotonia in REM sleep with awakenings. The patient awakens from sleep during the night, was in a REM phase, and cannot move because he/she continues to be hypotonic. But respiration is ostensibly unaffected, and eye movements can occur, and males may be erectile. Patients should be reassured about the mechanism and that they are not safe during these episodes and not about to die, because such happenings otherwise could be very frightening.

Hypnagogic and hypnopompic phenomena: Again, hypnagogic experiences may be linked up with the onset of REM prior to fully sleeping. I seldom encounter hypnopompic phenomena. These both are often predominantly visual, do not respond to atypical neuroleptic, and involve more distortions with illusions than hallucinations. The patient may have had them before, and education about them can take away the sense of fright, they may otherwise experience.

Table 9A: Features of Narcolepsy: Classically there is a quartet.

Next I describe features that are often not asked about. Double vision is again non-specific, but so is insomnia. However, the insomnia is a key symptom if patients are

having narcoleptic sleepiness during the day, they must have insomnia. Therefore, treatment for insomnia at night with medications must be carefully considered.

Importantly, these are often not recognized.

Diplopia: Double-vision is a common accessory symptom. But eye movements should be spared and this therefore should not be associated with cataplexy, so the symptom is strange [23,30,70,71].

Nocturnal insomnia: This is very common and classically explained by the narcoleptic still having 7-8 hour per day sleep cycles but their micro-sleeps during the day produce less need for sleep at night [23].

Table 9B: Secondary features of narcolepsy.

The difficulty with narcolepsy is the concurrent morbidity.

Often the hallucinatory (usually visual) episodes or visual illusory distortions are misinterpreted. Patients are then given high doses of neuroleptic and get worse. Some end up in

mental hospitals, sometimes for prolonged periods, because they get worse. And they are theoretically far more likely to be at higher risk than for tardive dyskinesia because they are biologically receiving inappropriate doses of neuroleptic for what are not true psychoses [14, 72-75].

Psychotic or psychopathological features: This occurs in about a quarter of patients and manifest differently from what one would expect. Narcolepsy is the great mimicker and we have several patients who were misdiagnosed and even may have ended up in mental hospitals [23].

Primary Dyssomnia. Commonly we see patients with gene expression and often with a loaded family history, yet no history of narcoleptic symptoms. Yet, we have never seen a patient who has no sleep disturbance after taking a detailed history, and yet this genetic expression. This leads us to postulate that there is a gene positive, primary dyssomnia group who manifests extreme fatigue, yet still responds to wakefulness drugs. The genetic expression is, therefore, non-specific primary dyssomnia with narcolepsy as the primary condition, but never in our experience has the patient been entirely without sleep disturbance. But then we do not evaluate "normal" individuals, usually so this is a biased population! [23]

Strange experiences: Though claimed otherwise, we have not seen more patients than the average population with out-of-body [76], near-death, or subjective paranormal experiences [23,77].

Table 9C: Variant extra features of narcolepsy.

Variants with gene expression

- a. About one third of our patients exhibit significant sleep disturbance. They may even have loaded family histories of narcolepsy (based on our experience and with the data available, this may be autosomal dominant). These patients might have significant primary sleep disturbances other than exhibiting narcolepsy. The gene then would reflect a dyssomnia, predominantly narcolepsy, but in these cases, other conditions.
- b. Some of our patients require a second hit (e.g. meningitis, in one instance, cysticercosis of the brain, head injury) to fully manifest.
- c. Many of our patients with narcolepsy but not cataplexy, have had MSLTs. However, they have had multiple sleep latency tests with a negative test. In our experience, and also at Cornell where I developed the NNQ in 1982-1983, it was not common to have a clean positive MSLT for narcolepsy, because patients' conditions are, in practice, complicated.
- d. We've seen two patients who are MSLT positive and yet genetically negative. This suggests there is more to Narcolepsy than just the gene, as well.

Pharmacological measures

- a. Invariably these patients respond to Wakefulness agents such as modafinil, armodafinil and sometimes to psychostimulants, partly and incompletely such as methylphenidate on its own, or as adjunct to the wakefulness drug.
- b. Unlike the early literature that claimed that the electroencephalogram is invariably normal, about half our patients with narcolepsy have temporal lobe foci, or are loaded with temporal lobe symptomatology and respond to anticonvulsants, in addition.
- c. The psychopathology commonly is controlled by additive buspirone for the agitation and anxiety, and/or atypical neuroleptic in low doses such as aripiprazole for the psychotic or paranoid features.
- d. The cataplexy responds well to tricyclics such as nortriptyline or clomipramine (sometimes obsessionality is common).

Finally I create Table 9D, effectively a flow chart to approach the possible narcoleptic patient.

Criteria sequence: Medical history taking then ESS + FISS, NNQ, HLA, responses, EEG if needed, MSLT and CSF unlikely unless atypical

1. Clinical symptoms

a. Key features:

1. EDS (excessive day-time sleepiness)
 2. Cataplexy
- b. Accessory
- Hypnagogic

Sleep paralysis

c. Extra likely

Diplopia

Insomnia

2. Clinical questionnaires to complete:

PNI Fatigue Severity Scale. (FISS-M) with Modified Epworth Sleepiness Scale

If scores on MESS are >10 (using the 8 questions 0 to 3 range) or if the MESS score is half or more of the FISS-1, then the Neppe Narcolepsy Questionnaire is completed.

Neppe Narcolepsy Questionnaire (NNQ)

3. HLA measures

Blood taken for narcolepsy HLA gene screening. It should include HLA DQB1* 0602 but also HLA DQA1*01:02 at minimum. If there are other issues, other HLA DQ protective genes should be prescribed. Supposedly the correlation of genetic HLA is in the 90%+ range with cataplexy with DQB1*0602 alone. But there are other genes: HLA-DQ6 (DQA1*0102) appears important and others such as HLA-DS15 (DRB1*15).

4. Pharmacological responsiveness if the diagnosis is clear or very likely

- a. Modafinil and armodafinil are mainstream treatments (varying doses)
- b. Methylphenidate or other stimulants if modafinil or armodafinil are not available and they are occasionally used as adjunct to them.
- c. Xyrem (oxybate), unusually, is prescribed, simply because it requires awakening at night to take a dose. Xyrem when used appears effective, and then used on its own.
- d. If cataplexy: Tricyclic antidepressant like nortriptyline e.g. 50mg to 75mg daily.

5. The Limitations of Esoterica:

- a. CSF Orexin or Hypocretin: Very rarely needed because it will just confirm what I know unless questions about etiology. Useful in research though and might lead to new drug development.
- b. MSLT and /or polysomnography: Useful in unusual cases, but expensive and low-yield in our group. But do not use this to decide whether wakefulness drugs are necessary.
- c. Electroencephalograms. In our experience at the PNI over 20 years, possibly one half of these patients have temporal lobe foci on extended monitoring. This contrasts with folk-lore where narcoleptic patients are supposed to have normal EEGs. If so the patients may require treatment e.g. Anticonvulsants.

Table 9D: The Practical Narcolepsy Ingredients (PNI).

I clearly see a loaded population. But it is difficult for me to believe the incidence of Narcolepsy is only one in 5000 patients. I suspect maybe 90% of narcoleptic patient diagnoses

are missed and if so the likelihood is the incidence is closer to 1 in 500. This marked underestimation of the narcoleptic population is also an opinion shared by Manzaneda [31] and also by Chakravorty who argues that “only 15-30% of narcoleptic individuals are ever diagnosed or treated, and nearly half first present for diagnosis after the age of 40 years [33].”

Applying the unified approach

Classifications of old are a problem: Type 1 Narcolepsy of old is now Narcolepsy with Cataplexy. Type 2 Narcolepsy of old is now Narcolepsy without cataplexy. Fortunately, the Type 1 and Type 2 labeling seems to not be as fashionable. As indicated, I would argue for a primary narcolepsy condition and for one that is symptomatic narcolepsy due to other causes such as infection or tumor impacting hypothalamic function.

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