Narcolepsy: A review amongst sleep disorders

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Abstract

Narcolepsy is a sleep disorder known and studied about from time to time is a sleep disorder characterized by a combination of myriad of symptoms including excessive day time sleepiness with recurrent irresistible sleep attacks, hypnagogic hallucinations, hypnopompic hallucinations, sleep paralysis and cataplexy (sudden and bilateral loss of muscle tone). Narcolepsy may present itself long with cataplexy or without cataplexy. The pathogenesis behind narcolepsy is found to be due to degeneration of hypocretin/orexin secreting neurons in the central nervous system due to disorder of human leukocyte antigen DQB1*0602. Narcolepsy is a debilitating disorder which causes intense functional impairment and hampers quality of life. Diagnosing narcolepsy can be challenging with help from clinical signs and symptoms, serum hypocretin/orexin levels and certain laboratory sleep tests. A definitive cure for narcolepsy is not known, but pharmacological therapy with certain lifestyle changes are the main options. Pharmacological therapy includes therapies like Modafinil and night time sodium oxybate. The purpose of this review is to provide an in-depth critical appraisal ship for the various treatment and diagnostic strategies for narcolepsy.

Introduction

Narcolepsy a REM sleep disorder is characterized by a tetrad of symptoms including excessive day time sleepiness with sleep attacks that start with REM sleep, hypnagogic hallucinations/hypnopompic hallucinations, sleep paralysis and cataplexy (an anticipated loss of bilateral muscle tone). The presentation is however variable and not all patient show the classic tetrad [2]. Other variable symptoms include blurry vision, loss of memory, loss of concentration, fragmented night sleep and automated behaviour [3-6]. Narcolepsy may be found in association with cataplexy or without and is associated with other sleep disorder like obstructive sleep apnoea and REM sleep behaviour disorder [7,8]. The epidemiology of narcolepsy is highly variable with prevalence of about 47/100000 in five European countries like Spain, Portugal, Italy, Germany and UK [9]. In counties like Japan and Israel the prevalence has been found to be 0.16% and 0.0002% respectively [10,11]. IN countries like US prevalence rates 19-56/100000 have been found [12]. The variances in prevalence could be attributed to the difference in the frequency of the HLA DQB1*0602 phenotype amongst the different geographical populations [13]. The data on incidence of narcolepsy is limited with 0.74/100000 persons-year with both narcolepsy with cataplexy and 1.37 per 100000 with both narcolepsy with cataplexy and narcolepsy without cataplexy with (1.72 for men and 1.05) for women. The incidence rate was highest in the second decade of life followed by third, fourth and fifth decades respectively [14]. Most cases of narcolepsy are sporadic with some with familial clustering. Environmental factors have also played a role with 25% to 31% concordance in monozygotic twins [15]. People who are first degree relatives are 10 to 40 times more vulnerable to develop narcolepsy compared to general population [16]. Recent studies have also established a close link between narcolepsy and streptococcal infections [17] and H1N1 vaccination [18]. About 85% people having symptoms of narcolepsy with cataplexy are positive for HLA DQB1*0602, often simultaneously with HLA DR2 (DRB1*1501) and only 50% with narcolepsy only have a positive HLA DQB1*0602 haplotype [19]. Some rare cases lack the classic HLA DQB1 [20]. However, there is lack of sufficient data in establishing routine HLA screening as a diagnostic test. Hypocretin 1 and 2 also known as orexin A and orexin B neurotransmitters produced by the hypothalamus help regulate sleep wake cycle [21] and deficiency is found associated with narcolepsy leading to abnormalities in REM sleep and excessive day time sleepiness [22]. Some receptor mutations such as mutated hypocretin receptor 2 have also been found [23]. Another important cause for narcolepsy is autoimmunity the details of which are mentioned as follows. The Tribbles homolog 2 (Trib2) transcript has been shown to be abundant in the hypocretin neurones of engineered mice [24].

Autoimmunity in narcolepsy

It has been established that people who lack the cells that produce hypocretin also known as Orexin, have Narcolepsy. Hypocretin, which is produced by the lateral hypothalamus, helps to regulate the sleep-wake cycles. The loss of 90% of hypocretin producing neurons leads to a significant decrease in hypocretin levels in the cerebrospinal fluid. Narcolepsy has been found to have a strong predisposition with MHC DQB1*0602 and T cell Receptor polymorphisms [25-28], that includes bystander activation and molecular mimicry. It is widely accepted the polygonal activation of the T-cells occurs subsequent to viral infections that creates a platform for the activation of T-cells that later on kill the neurons involved in the synthesis of hypocretin(orexin) in the hypothalamus. This might be due to Bystander activation in which the Epitope of the hypocretin-producing cells might trigger an autoimmune response. The MHC DQB1*0602 is hypothesized to be

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processed and presented (by molecular mimicry) and could activate the T-cells in predisposed individuals. There are various mechanisms by which infections can lead to an initiation of an autoimmune event but in the case of narcolepsy, no concrete evidence has been postulated.

Professor Emmanuel Mignot (a professor of Psychiatry at Stanford University) was the first to discover that Narcolepsy was caused by a loss of hypocretin synthesizing neurons. The exact etiology is still unknown but many evidences points out that the disease has an autoimmune linkage. One evidence was the presence of genetic predisposition to autoimmune disease in patients with narcolepsy with human leukocyte antigens (HLA). In addition to this a second phenomenon which is present in all autoimmune disease was discovered: A triggering or Inciting event. Over the past decade an increase in narcolepsy after an Influenza H1N1 infection and its vaccination strongly supports the disease's autoimmune etiology. This became clear when researchers from multiple countries found the incidence of narcolepsy following vaccinations with Pandemrix against the H1N1 strain of influenza in 2009. The results showed that there was a three-fold increase in incidence in Sweden [29] and a 12-fold increase in incidence was recorded in Finland [30]. Other countries like England [31], Norway [32] and France [33] also showed significant rise in the incidence of Narcolepsy.

A study in 2011 which was co-authored by Mignot also showed increased incidence of Narcolepsy showing a 3-fold increase in china following a flu vaccination which he had mentioned and published in his Annals of neurology. He also said that nearly 98% of the narcoleptics had associations with HLA genes that are only known to be found in 25% of the world's population [34]. However, no rise in incidence was recorded in the USA following Pandemrix vaccination [35].

The disease has a high prevalence in the spring or summer and rarely during winter. This pattern as suggested by Prof. Mignot, postulates narcoleptic patients who are vaccinated in the winter season initially have a normal response but towards the summer develop a response that involves extensive killing of hypocretin-producing cells in the hypothalamus.

However, having said all this, researchers are yet to find a confirming proof that Narcolepsy is indeed an Autoimmune disease. That missing link might be the antibodies or the cells that attack the hypocretin-producing cells in narcoleptic patients. Professor Thomas Scammell in Harvard Medical School in Boston, Massachusetts also further explained that we currently also do not know as to how exactly the hypocretin-producing cells are being killed or attacked.

Discussion

Diagnosis

Narcolepsy is not a common sleep disorder, but researchers and clinical physicians have had some difficulty of diagnosing this sleep disorder. Narcolepsy is characterised by tetrad of symptoms:

1. Excessive daytime sleepiness (EDS)-episodes of excessive sleepiness experienced throughout the day comparable to how one would feel after staying awake for more than 48-72 hours.

2. Cataplexy—sudden onset of muscle weakness that is often triggered by strong emotions resulting in inability to move upon awakening. The weakness experienced is usually jaw slackening or head dropping and emotions that trigger such muscle weakness includes elation, surprise or anger.

3. Sleep paralysis that varies from a few seconds to minutes. The patient is usually unable to move while going to sleep or upon awakening.

4. Hallucinations occur while falling asleep(hypnagogic) or awakening from sleep(hypnopompic). These can be visual, auditory or tactile in nature.

However, it has been known and established that hallucinations and sleep paralysis are highly variable features and may or may not be present in a significant number of narcoleptic cases.

Other symptoms also found in narcolepsy, but not classically associated with it are:

1. Restlessness while going to sleep
2. Hyperactivity which has been observed mostly in narcoleptic children
3. Automatic behavior or unconsciousness in which the patient is unaware of his/her actions.

Individuals thought of having narcolepsy are advised by their primary care physicians to see a sleep specialist in sleep centres where the disorder is mostly diagnosed using Two tests: The polysomnogram or the multiple sleep latency test.

1. The PSG (Polysomnogram) requires the patient to sleep overnight at the sleep centre during which the test records the level of brain activity, heart rate and the blood pressure. A PSG study can tell a patient of how quickly he/she falls asleep, the onset of REM (Rapid eye movement) as soon as the patient fall asleep and how often he/she wakes up during the sleep cycle.

2. A Multiple sleep latency test is a daytime sleep study (vs a PSG) and hence measures the level or the intensity of sleep the patient is in. A person is made to sleep for every two hours for a duration of 20 mins every time and the technician tells how quickly a person is able to fall asleep, at what time different stages of a sleep cycle are encountered and exactly how sleepy a person is upon awakening.

3. The Hypocretin level measurement was a test the measured the level of hypocretin but is no longer used in the diagnosis of narcolepsy since it requires a lumbar puncture (spinal tap) to be performed. It was used to show low levels of hypocretin which was diagnostic of narcolepsy Type 1 irrespective of the presence or absence of cataplexy.

Treatment

Narcolepsy is a lifetime sleep disorder and narcoleptic patients may have to be on a lifetime treatment. A number of treatment modalities for this uncommon disorder have been proposed and used. These modalities have been categorised into Nonpharmacologic and pharmacologic based on the onset, duration and frequency of the features of this disorder.

Non-pharmacological approach to narcolepsy

One of the most important aspects of the treatment for narcolepsy is Sleep hygiene. This comprises of having regular sleep of 7.5-8 hours of sleep as well as having regular timed naps during the day. Adults with Narcolepsy need to have special consideration such as being provided with emotional support and counselling to both the patient and their attendants. They should be questioned and evaluated for possible cases of Alcohol or drug abuse that can have a potentiating effect on the symptoms of Narcolepsy. Patients should also be inquired about any
possible psychosocial problems like family conflict, depression or a family history of depression or any family conflicts which can affect the duration or the severity of symptoms as well. Workaholics should be advised to avoid having jobs that require long hours of labour or official work. They should be advised to have scheduled naps prior to long drives. Heavy food and alcohol intake should also be minimized as they can induce sleep hence exacerbating and worsening the EDS.

Counselling should be offered to narcoleptics as many patients are often found to have coexisting depression and many have a fear of falling asleep at inappropriate times that can trigger anxiety and uncomfortable sensations.

Broughton and Murray had mentioned in their study in 2006, that certain behavioural stimulation had been successful in 6 out of 13 patients. Such behavioral simulation included patient positional changes such as standing rather than sitting, movement in their daily routines, going out into the external environment, having a cooler environment and a louder and more lively environment with a higher background noise [36].

Studies over the years have shown that smokers take an extensive time frame to fall asleep hence, narcoleptics should be offered ways to reduce smoking or should be offered appropriate substitutes [37].

Children with narcolepsy may need to be monitored with some care as well. Avoidance of food or beverages rich in refined sugars has shown to reduce daytime sleepiness. Activities should be avoided if they are observed as being drowsy. However, on an everyday routine, children should be encouraged to participate in sports and physical activities and hence, a well-designed exercise program should be devised to reduce the occurrence of the symptoms of this disorder amongst adolescent and teens.

Patients should be advised to have and follow strict napping for 15-20 minutes 2 to 3 times per day. Other techniques that can be useful are manipulation of the temperature of body/skin (keeping the extremities cooler can be useful), consumption of hot food or beverages during daytime. CBT (Cognitive Behavioral Therapy) can be useful as it targets the behavioral symptoms of narcolepsy. It has been found to be very effective in treating medication non-adherence and noncompliance. Features like depression and hypersomnia is being successfully treated by CBT [38,39].

**Pharmacological treatment**

The management of narcolepsy is primarily based on the symptomatic presentation of the patient. The most commonly found symptom of narcolepsy is Excessive daytime somnolence that can lead to automobile accidents and even death due to a massive injury.

Hence, drugs that combat EDS are commonly prescribed such as Modafinil and Sodium Oxybate that promote wakefulness by targeting the neurotransmitters such as dopamine and norepinephrine as well as antihistaminic pathways. They increase the levels of dopamine that leads to increased wakefulness time that can counteract the EDS [40,41]. Some studies conducted on a larger scale have shown that Modafinil has been successful in treating feelings of sleepiness in narcoleptic patients which was quantified on the Epworth Sleepiness Scale. Modafinil also helped to improve the wakefulness in patients which was recorded on the Maintenance of Wakefulness test [42,43].

Unlike Modafinil, Sodium oxybate is a relatively newer medication also known as GHBA (GABA hydroxybutyric acid) and is very effective in treating EDS as well as cataplexy. It is reported to improve the quality of nocturnal sleep that leads to improved daytime hours. It has been reported to markedly reduce the number of sleep attacks and sleep paralysis as well by increasing slow wave sleep, but similar to stimulants it has been associated with abuse, withdrawal side effects and dependence [40,41,44-48]. Studies performed over the past years on a large number of patients have shown that sodium oxybate has 4 successful in reducing cataplexy by 70-85% [46].

Stimulants (Amphetamines and Dextromethorphan and in some cases Methylphenidate) are used as an ancillary treatment for narcolepsy in cases when the first line treatment is no longer effective. They enhance alertness by altering the monoaminergic pathways specifically targeting dopamine and norepinephrine. However, these stimulants can cause potential side effects such as arrhythmias, psychiatric disturbances and addictions. Hence, for these reasons they are primarily prescribed for treating Disorders with attention deficits (ADHD) or impulsiveness. Methylphenidate has also been associated with weight loss and insomnia and cannot be prescribed to anorexics or bulimics [49].

**Conclusion**

The article therefore provides a snapshot on the pathophysiology and the various treatment options available for narcolepsy further reviews and article can aid understanding this sleep disorder in detail especially in relation with other chronic disease.

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