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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 , hypnogogic hallucinations ,hypnopompic hallucinations ,sleep paralysis and cataplexy (sudden and bilateral loss of muscle tone).¹ Narcolepsy may present it self long with cataplexy or without cataplexy. The pathogenesis behind narcolepsy is found to be due to degeneration of hypocretin/orexin secreting neurones 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.

INTRODUCTION

Narcolepsy a REM sleep disorder is characterized by excessive day time sleepiness.The presentation is variable and not all patient show the classic tetrad².Variable symptoms include blurry vision, loss of memory ,loss of concentration ,fragmented night sleep and automated behavior.^{3,4,5,6} Narcolepsy may be found in association with cataplexy or without and is associated with other sleep disorder like obstructive sleep apnea and REM sleep behavior 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 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 sleepiness²².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 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 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 infections¹⁷ 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.

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-wave 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*06:02 and T cell Receptor polymorphisms²⁵⁻²⁸ that includes bystander activation and molecular mimicry.

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. 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 phenomena 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 Sweden²⁹ and a 12-fold increase in incidence was recorded in Finland³⁰. Other countries like England³¹, Norway³² and France³³ 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 population³⁴. However no rise in incidence was recorded in the USA following Pandemrix vaccination³⁵. However, having said all this, researchers are yet to find a confirming proof that Narcolepsy is indeed an Autoimmune disease..

DISCUSSION:

Diagnosis; Narcolepsy is not a common sleep disorder but researchers and clinical physicians have had some difficulty of diagnosing this sleep disorder. Individuals thought of having narcolepsy are advised by their primary care physicians to see a sleep specialist in sleep centers 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 center 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. Treatment modalities have been categorised into Nonpharmacologic and pharmacologic options based on the onset, duration and frequency of the features of this disorder.

1. 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,. Family conflict, depression in the family can also have a potentiating effect on the symptoms of Narcolepsy.. 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. Broughton and Murray had mentioned in their study in 2006, that certain behavioral stimulation had been successful in 6 out of 13 patients. Such behavioral stimulation 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 noise³⁶. 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 high in refined sugars has shown to reduce daytime sleepiness. Participation in sports and physical activities is advised 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 helpful techniques include 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}

2. 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.^{40,41,42}. 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.^{43,44}. Unlike Modafinil, Sodium oxybate is a relatively newer medication also known as GHB (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.^{40,42,45,46,47,48,49}. Studies performed over the past years on a large number of patients have shown that sodium oxybate has been successful in reducing cataplexy by 70-85%.⁴⁷. 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.^{50,51}.

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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Muhammad Umer Ahmed; concept, data collection, data analysis, manuscript writing, manuscript review

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