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Invited Review

Approach to Narcolepsy - A Rare but Potentially Treatable Sleep Disorder!

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Abstract

'Narcolepsy' comes from French narcolepsie, which was first used by French physician Jean-Baptiste Edouard Gelineau in 1880. This French word came from a combination of Greek narke, meaning stupor or numbness, and lepsis, meaning a seizure. The tetrad of narcolepsy symptoms proposed by Yoss., et al. in 1957 consists of excessive daytime somnolence, hypnogogic hallucinations, sleep paralysis and cataplexy [1]. Narcolepsy is a chronic neurologic condition due to dysregulation of sleep wake cycle, affecting 1 in 3000 individuals with a bimodal peak of incidence at 15 and 36 years of age [2]. However, there is a diagnostic delay inspite of early age of onset partly due to limited awareness of this entity among physicians and partly due to the associated comorbidity burden among patients with Narcolepsy [3].

Keywords: Narcolepsy; Cataplexy; Hypocretin; SOREMPs; MSLT

Diagnostic Criteria

Narcolepsy was historically classified based on symptoms into Narcolepsy with or without cataplexy. With the establishment of Hypocretin theory [5]. in the pathogenesis of Narcolepsy, a small subset of individuals may present without cataplexy at the onset, but may eventually do so and hence, the terminology of 'Narcolepsy with cataplexy' needed revision. The International criteria for Sleep disorders (ISCD). - third edition, classifies Narcolepsy into Type 1 and Type 2 [4].

International criteria for sleep disorders (ISCD). - third edition - classification of narcolepsy

Narcolepsy Type 1
CSF Hypocretin - 1 deficiency (110 pg/mL or less than 1/3rd of the normative values with the same standardised assay).
Mean latency of < 8mins on Multiple Sleep Latency Test (MSLT). with evidence of sleep onset REM periords (SOREMPs). fulfilling - Either 2 SOREMPs on MSLT (or). 1 SOREMP on PSG along with 1 SOREMP on MSLT
Cataplexy - defined as more than one episode of brief (< 2mins)., usually bilaterally symmetrical, sudden loss of muscle tone with retained consciousness

Table a

Narcolepsy Type 2
CSF measured, should not meet criteria as Type 1
Mean latency of <8mins on Multiple Sleep Latency Test (MSLT). with evidence of sleep onset REM periords (SOREMPs). fulfilling - Either 2 SOREMPs on MSLT (or). 1 SOREMP on PSG along with 1 SOREMP on MSLT
Absence of Cataplexy

Table b

Symptoms of narcolepsy

The tetrad of symptoms are manifested due to imbalance in transition between sleep and awake as well as transition between REM and non-REM sleep. Only 10-15% of individuals present with all 4 characteristic symptoms [9].

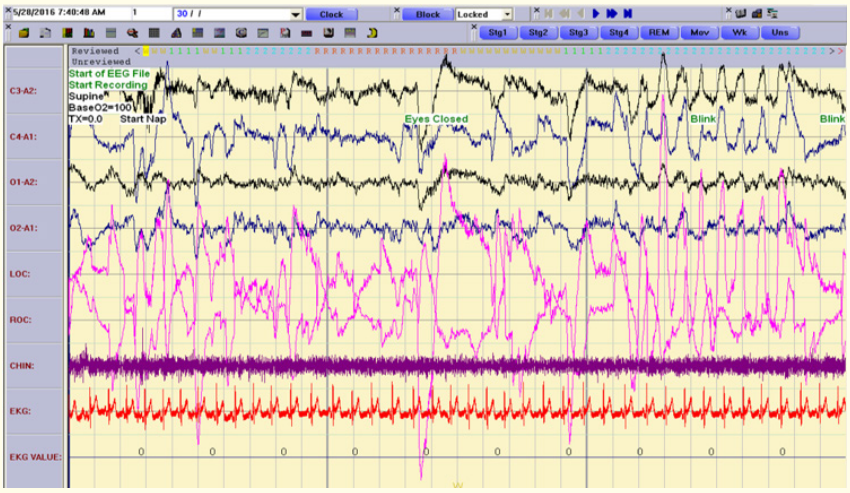

Figure 1.1: Shows initial recording in awake state at 7.40.48 AM, evidenced by eye blinks and eye movement artefacts (red arrow).

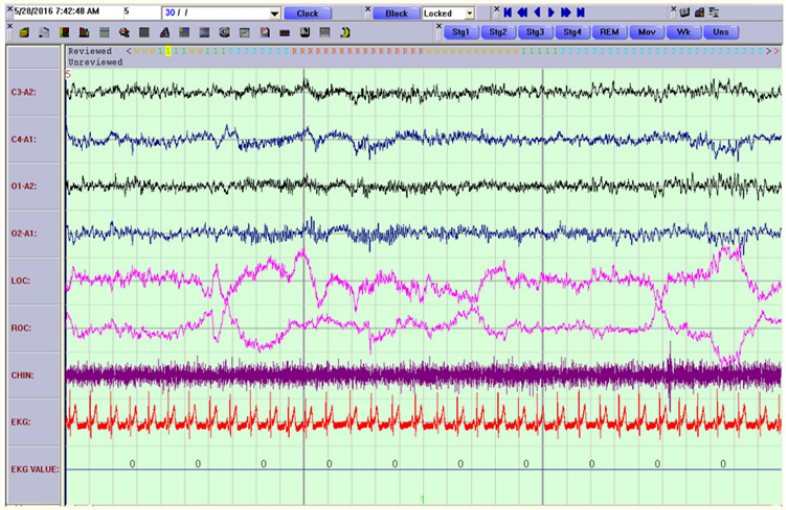

Figure 1.2: Shows onset of sleep at 7.42.48 in the same patient, which has a onset in 2 minutes.

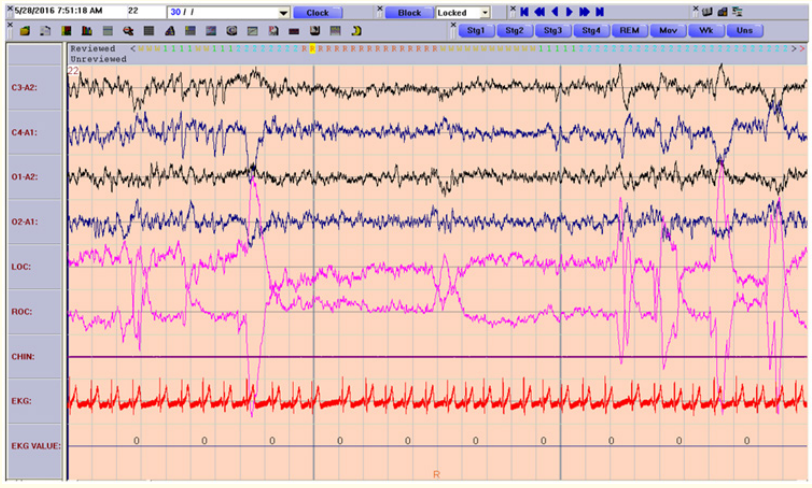

Figure 1.3: Shows onset of REM sleep at 7.51.18 AM, as evident by rapid eye movements (black arrow) seen in oculogram recording and lasts for atleast 15 seconds in this epoch. REM sleep is latency is calculated from beginning of first epoch with sleep onset to first epoch with REM sleep, which is here 9 minutes 30seconds.

Excessive day time sleepiness

This is usually the first manifestation of Narcolepsy. Individuals initially find difficulty in listening to lectures at school, work place or doing sedentary activities due to excessive sleepiness inspite of an adequate refreshing night time sleep. However, medical attention is not sought until the severity worsens to show a considerable fall in performance grade or a Motor vehicle accident. This is a mandatory criteria which should be present on a daily basis for at least 3 months for diagnosis of Narcolepsy [8]. Patients feel asleep for few seconds to minutes and then feel refreshed after the nap. Sleepiness may be subtle as constant sleepiness with occasional exacerbations or a frank sleep attack. However, the total sleep time per 24 hours is normal or only slightly increased due to associated nocturnal sleep maintenance insomnia.

Hallucinations

It occurs in 30-60% of patients with Narcolepsy and about 20% of general population. It may occur at the onset of sleep (hypnogogic). or during awakening from sleep (hypnopompic). It may be bizarre or comforting, usually visual, but may be sensory or auditory [9]. Typical hallucination in Narcolepsy includesa sense that a threatening stranger is in the bedroom or that one is being attacked by animals, however auditory hallucinations and fixed delusions are unlikely to occur in Narcolepsy.

Sleep paralysis

It occurs in 10-15% of patients during sleep onset or offset as either partial or complete, accompanied rarely by asphyxiating feel although respiratory muscles are spared.

Cataplexy

This symptom occurs almost exclusively in about 60-70% of patients with type 1 Narcolepsy. This symptom characteristically occurs 3-5 years after the onset of excessive day time sleepiness, but rarely precedes it [11]. It is usually triggered by sudden emotions either positive or negative or can occur spontaneously on rare occasions. It is characterised by sudden onset, rapidly progressive, reversible, partial or complete paralysis of the voluntary muscles beginning from face, neck, trunk and the limbs except diaphragm and extra ocular muscles and evolves over a period of few seconds causing the patient to slump to the ground to lie fully conscious but immobile for about 1 to 2 minutes. The attacks may rarely be accompanied by motor phenomenon such as twitching of face or limbs and urinary incontinence. During cataplexy attack, deep tendon reflexes are diminished and electrophysiologically H waves are absent.

Patients with Narcolepsy have a tendency to gain excess weight probably due to low metabolic rate and the BMI is adult patients

15% above average. Sleep disorder breathing and periodic limb movements are found to be associated in patients with Narcolepsy with cataplexy. REM sleep behaviour disturbances in younger adults especially females was found to be forerunner of Narcolepsy [10]. Narcolepsy is associated with cognitive deficits in executive domains due the reduction of available cognitive processing resources as there is continuous demand of resources for monitoring and maintenance of vigilance [12]. This disorder is also associated with high burden of medical and psychiatric comorbidities, which include hyper cholestrolemia, disorders of digestive system, heart disease, upper respiratory tract infections, hypertension, major depressive disorder and social anxiety disorder [13]. The partial loss of hypothalamic hypocretin neurons is found to be associated with anosmia in patients with narcolepsy with or without cataplexy [14]. One of the rare association of Narcolepsy would be an underlying brain pathology like demyelination, hypothalamic tumour, head injury or a vascular disease [15].

Diagnostic testing

The diagnostic testing for Narcolepsy involves an overnight polysomnography and multiple sleep latency test (MSLT). Polysomnography is done to rule out alternate causes of excessive day time sleepiness. Multiple sleep latency test is a cornerstone to the diagnosis, which is performed based on the following recommendations [16].

- The study should begin 1.5 to 3 hours after the completion o overnight polysomnography
- Five nap opportunities are provided at 2 hour interval
- Sleep rooms should be dark and quiet with ambient room temperature
- Medications with stimulant or sedating property must be withheld at least 2 weeks prior to testing
- Smoking must be abstained at least 30minutes prior to each nap opportunity and vigorous physical activity must end at least 15 minutes prior to the nap opportunity
- A light breakfast is recommended 1 hour prior to first nap opportunity and a light lunch is recommended immediately after the end of second noon trial
- The recoding montages for MSLT includes central EEG (C3-A2, C4-A1). and occipital (O1-A2, O2-A1). derivations, left and right eye electrooculograms (EOGs)., mental/submental electromyogram (EMG)., and electrocardiogram (EKG) (Figure 1.1).
- Prior to each nap, the patients are given standard instructions to lie in a comfortable state.
- Sleep onset is defined as the first epoch of greater than 15 sec of cumulative sleep in a 30-sec epoch (Figure 1.2).
- The nap session is terminated at 20 minutes if sleep does not occur. The absence of sleep on a nap opportunity is recorded as a sleep latency of 20 minutes. This latency is included in the calculation of mean sleep latency (MSL).
- In order to assess for the occurrence of REM sleep, the test continues for 15 minutes (clock time). after the first epoch of sleep.
- REM latency is taken as the time of the first epoch of sleep to the beginning of the first epoch of REM sleep regardless of the intervening stages of sleep or wakefulness (Figure 1.3).
- The MSLT report should include the start and end times of each nap opportunity, latency from lights out to the first epoch of sleep, mean sleep latency (arithmetic mean of all nap opportunities)., and number of sleep-onset REM periods (defined as greater than 15 sec of REM sleep in a 30-sec epoch).

However, MSLT has high false positive and false negative results. About 6% normal males and 1.5% normal females may have a MSLT diagnostic of Narcolepsy [17].

CSF hypocretin levels

CSF studies for low Hyprocretin-1 levels may be indicated in patients with inconclusive MSLT. About 90% of individuals with narcolepsy with cataplexy and about 20-30% of individuals with narcolepsy without cataplexy may have a low hypocretin-1 levels, which is defined as < 110 pg/mL.

Pathophysiological aspects of narcolepsy

Hypocretins (orexins). are peptide neurotransmitters produced by neurons of lateral hypothalamus, which are produced during wakeful state to stimulate neurons of cortex, including basal forebrain, hypothalamus and brainstem to produce wakefulness. In addition, hypocretins also increase the activity of regions that suppress REM sleep, increases metabolic rate, sympathetic tone and facilitates rewarding behavior. The selective loss of 85-95% of hypocretin producing neurons in hypothalamus forms the basis of narcolepsy with cataplexy [20]. Narcolepsy without cataplexy is caused due to partial loss of hypocretin neurons [21]. The cause for selective loss of hypocretin producing neurons is uncertain,

but a strong association with HLA DQB1*0602 haplotype, which is found in about 95% of patients with type 1 narcolepsy and 40-60% in type 2 narcolepsy. The individuals with HLA DQB1 * 0602 are found to be at 251 times higher risk of developing narcolepsy [22]. Narcolepsy is usually sporadic, and the risk that an affected parent will have an affected child is only 1%. When one monozygotic twin has narcolepsy, there is only about a 30% chance that narcolepsy will develop in the other twin. It is found that a combination of genetic factors and environmental factors like upper respiratory tract infection would lead to dysregulated immune mechanisms and destroy hypocretin neurons selectively by way of molecular mimicry [23]. However, damage to hypocretin neurons may occur as a result of demyelination, stroke, tumor, paraneoplastic disease or granulomatous disease and lead to symptomatic narcolepsy.

Differential diagnosis

- Conditions that can mimic Narcolepsy without cataplexy
- Obstructive sleep syndrome
- Periodic limb movement disorder
- Idiopathic hypersomnia - longer duration of sleep naps
- Pharmacologically induced sleepiness
- Behaviourally induced inadequate sleep syndrome
- Depression - hypersomnolence with shortened REM latency

Cataplexy like attacks

- Pseuocataplexy, functional disorder
- Niemann pick disease C [28].
- Coffin Lowry syndrome [29]., stimulus induced drop attacks, mental retardation, facial and skeletal abnormalities.
- Hypereklepsia [30].

Management general measures

Patient with narcolepsy must engage in jobs that provide constant stimulation instead of sedentary life style. The major intervention would be to ensure a good quality night time sleep and addressing associated sleep disorders if any. A short timed - nap during daytime for 15-20 minutes may be helpful.

Modafinil

It acts by reducing the reuptake of dopamine and is considered as a 'wake promoter'. It significantly increases the mean sleep latency time, reduces the number of daytime sleep episodes and periods of severe sleepiness. It does not interfere with the patients' ability to nap voluntarily during the day and also with the quantity and quality of night time sleep. It has a elimination half life of 10-15 hours and is well tolerated at dose of 200mg per day for excessive day time sleepiness and has a low addictive potential though higher dose may be associated with severe nausea and anxiety [24].

Amphetamines

Amphetamines like methyl amphetamine and dextroamphetamine blocks the reuptake and increases the release of dopamine along with serotonin and nor epinephrine to a lesser extent. The major side effects are hypertension, cardiac, psychiatric and addictive effects. Dexamphetamine has a half life of 6-10 hours and it is started at a dose of 5 mg twice daily to a maximum of 60 mg per day.

Antidepressants

Cataplexy is addressed with a low dose of antidepressant. Clomipramine and Venlafaxine are approved to be anticataplectic drugs. Fluoxetine is also an effective alternative.

Sodium oxybate

Sodium Oxybate is a newly licensed drug for cataplexy and excessive daytime sleepiness, which probably acts as $GABA_A$ receptor agonist. It is available as a liquid, taken at bed time and 2.5 to 4 hours later. The major limitation of sodium oxybate is its high cost and being highly sedative, it can cause severe respiratory depression and it is used by criminals as a date-rape drug.

Experimental drugs

In young patients with severe and acute presentation of Narcoleptic symptoms were tried with IVIG, considering the possibility of underlying autoimmune possibility. However, a favorable outcome was not found in all the individuals [25]. Hypocretin agonists has been found to abate narcolepsy symptoms in animal models [26]. Other drugs in exploration are histamine antagonists and melanin-concentrating hormone receptor antagonists [27].

Conclusion

'An entity is rare only until its identity is rare', holds to the under diagonsis of Narcolepsy, partly due to the long-drawn course of the disease especially with cataplexy not being the initial presentation usually and also due to the associated comorbidities in patients

with Narcolepsy. However, on the other hand, a over diagnosis of Narcolepsy remains a complication of a specialist centre due to the overlap of most of the clinical features with other common conditions. A careful history and appropriate laboratory testing must be made to identify and create Narcolepsy at the earliest in view of its potential complications in physical, psychological and social consequences.

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