Review Article

Narcolepsy in Children

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INTRODUCTION

Narcolepsy is a unique and distinct disorder of sleep which on one hand amuses and allures us into its multifaceted clinical and polysomnographic presentations and at the same time evades early and accurate diagnosis because of the gap in knowledge even among well trained medical personnel.

Patients with narcolepsy have a misplaced REM sleep which attempts to precede other stages of sleep and often succeeds and even disturbs wakefulness by its frequent intrusions. This intrusion can bring along the associated muscle atonia of REM sleep causing patients to lose their balance and fall, an event often precipitated by laughter or other emotional stimuli. This phenomenon is referred to as cataplexy. However, narcolepsy can occur without cataplexy also. The other manifestations include hypnogogic hallucinations and sleep paralysis.

The disease has an estimated prevalence of 26 to 56/100000 in the general population but there is also sufficient evidence from literature to suggest that this is only the tip of the iceberg. The disease has a bimodal peak with a significant proportion occurring in the pediatric age group especially adolescence.[1] The disease hampers the personal, academic/professional and social life of those affected and children are no exception.

DIAGNOSTIC CRITERIA

The pentad of narcolepsy comprises of excessive daytime sleepiness, cataplexy, hypnagogic/ hypnopompic hallucinations sleep paralysis and disturbed nocturnal sleep is seldom fulfilled in an individual patient. When the pediatric population is considered, the clinical picture is further confounded by clinical mimics and a variety of other factors both clinical and socio-cultural. Polysomnographic features like reduced mean sleep latency and sleep onset REM periods on MSLT are also not by themselves and exclusive feature of narcolepsy being found even in patients taking antidepressants and those with sleep apnea. This leads to a delay in diagnosis which can vary from months to years. Hence the diagnosis should be based on more sensitive but objective criteria. The two most widely used criteria for diagnosis of narcolepsy are the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) and International Classification of Sleep Disorders Third Edition (ICSD-3.

According to DSM-5, a confirmatory diagnosis of narcolepsy is made when excessive day time sleepiness (EDS) is associated with any one of the following: (1) cataplexy; (2) CSF hypocretin deficiency; (3) REM sleep latency ≤15 minutes on nocturnal polysomnography (PSG); or (4) mean sleep latency ≤8 minutes on multiple sleep latency testing (MSLT) with ≥2 sleep-onset REM-sleep periods (SOREMPs). On the other hand, ICSD-3 criteria requires 1) cataplexy and either positive MSLT/PSG findings or CSF hypocretin deficiency; (2) MSLT criteria is similar to DSM-5 except that a SOREMP(within 15 minutes of sleep onset) in the previous night PSG is also counted to fulfill the requirement of 2SOREMPS (3) Sub classification of narcolepsy into type 1, which denotes the presence of cataplexy or documented CSF hypocretin deficiency, and type 2, where cataplexy is absent while CSF hypocretin levels are either normal or undocumented.

Epidemiology

Narcolepsy is not a widely reported phenomenon in young children and hence could be regarded as a rare occurrence. Having said that the most common age group affected are the adolescents. Taken in toto, 50% of patients have clinical onset less than 15 years. The scenario however has significantly changed at least in some parts of the world after the recent pandemic of H1N1. Some countries like Finland and Sweden had the most profound impact with a 17- and 25-fold rise in pediatric cases while others like China, Switzerland Germany and Denmark showed a comparatively less alarming albeit significant trend towards this disturbing shift. In the wake of this evolving epidemiological pattern, one needs to especially consider the diagnostic hurdles and prognostic repercussions unique to this age group.

Pathophysiology

Over the last decade, there has been a lot of advances into our understanding of what causes this perturbation in sleep wake cycle and the hypothalamic peptide hypocretin stands at the center stage of most of its pathophysiologic cascades. Autoimmune pathways triggered by infections, vaccination or other environmental factors lead to destruction of hypocretin secreting neurons in the hypothalamus, a process arguably facilitated by genetic predisposition in the individual. The latter theory has been supported by the presence of the HLA allele 1 DQB1*0602 in narcoleptic subjects. The presence of an affected family member increases the chance of disease by 10-40 times while the concordance rate in identical twins is only 32%. Hence, narcolepsy can be viewed as prime example of a disease where genetic and environmental factors play a equally important role with significant inter-relationship between the two.

HLA class II molecules (DR, DQ, DP) are present on the surface of B cells, macrophages and dendritic cells which execute their antigen presenting function by forming heterodimers. The cells with heterodimeric combination that causes autoimmunity to cells are selectively destroyed by organs like thymus and bone marrow. When some of these cells with heterodimers between HLA DQ 0602 and 0601 are present in a person, he or she is likely to present self-antigens to T cells which ultimately result in loss of hypocretin neurons. These neurons are depleted to the tune of 90-95% in autopsy brain specimens of narcoleptic subjects with exquisitely preserved neurons even within the hypothalamus. Hypocretin secreted by neurons in the hypothalamus have rich cortical and subcortical structures especially those in the midbrain. Thus, the deficiency of hypocretin indirectly converts into reduced excitatory input to the wake-promoting centers which culminates in excessive daytime sleepiness. Functional neuroimaging studies using Positron emission tomography (PET), single photon emission computer tomography (SPECT) and cerebral perfusion scans have demonstrated dysfunction of a wide network involving limbic, deep gray and cingulate-prefrontal and motor-sensory cortical structures along with hypothalamus.

Recently, the role played by humoral immune mechanisms have come to light with the discovery of anti -tribbles homolog -2 antibodies (TRIB-2) in narcolepsy by Czvetkovic-Lopez et al. These are self-antibodies directed against a protein widely expressed in the brain but may selectively affect

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hypothalamic control of sleep wake cycle resulting in narcolepsy with cataplexy. These antibodies are more frequently associated with a shorter duration of disease and has a dubious link with ASO positivity and hence past streptococcal infection. T cell alpha receptor polymorphisms are also associated with narcolepsy.

Diagnostic considerations

Sleepiness in children by itself does not draw much attention in many cultures and is often attributed to weather or poor diet or general slowness. Many times, it leads to ridicule from peers and kin but rarely to medical evaluation or treatment. By 3-5 years of age, the sleep wake cycle becomes established in a child and daytime napping ceases to be part of their routine. However, this is a slow process that continues into adolescence and some children in the early second decade tend to have a physiological tendency to sleep more during day. Moreover, some of them have a habit of sleeping late which is acquired during childhood or even during adolescence. REM sleep may occupy upto half of the sleep-in newborns and sleep onset REM periods (SOREMPS) may be seen in normal children aged less than three months. The adult pattern of 25% REM sleep and REM latency of 90 minutes is gradually attained by the end of first decade.

The clinical features of narcolepsy are more or less like those seen in adults with some essential differences. Children with narcolepsy tend to be more sleepy which some authors think are a reflection of them having a more severe form of narcolepsy resulting in an earlier age of onset. Some children will be labelled as “a habitually sleepy child” without any clear demarcation between normalcy and onset of symptoms. Children also are more likely to lack the classical triad and monosymptomatic presentation as excessive daytime sleepiness can pose a diagnostic challenge. Other cardinal manifestations may evolve over time .To complicate things further, victims may have paradoxical hyperactivity, irritability and or confessional arousals during night. This can lead to misdiagnoses of epilepsy or attention deficit hyperactive disorder or other neurobehavioral problems. There is also higher incidence of depression, nocturnal eating, obesity, and emotional issues in children compared to adult. Disturbed nighttime sleep leading to hormonal imbalances coupled with nocturnal and or emotional eating may predispose patients to weight gain. Excessive sleepiness and fatigue and disinclination to participate in outdoor sports due to both social and physical factors may result in a sedentary lifestyle and consequent obesity. There are few anecdotal reports of symptomatic polycystic ovaries and metabolic syndrome being associated with secondary narcolepsy. Vgontzas has reported a very high incidence of excessive daytime sleepiness (80%) in patients with PCOS, an observation that needs to be explored in detail. Quality of nocturnal sleep is an overlooked aspect of narcolepsy. Recent reports have revealed that affected patients have insufficient nighttime sleep despite a preserved or reduced sleep onset latency. This is because of repeated arousals which can occur both from slow wave sleep as well as from REM sleep along with intermittent awakenings. These episodes are usually brief but prolonged awakening can also occur.

Cataplexy as we know it in adult description evolves over time in the pediatric age group. The initial phase is characterized by excessive day time sleepiness, early bedtime, delayed waking time and other features of EDS followed by more generalized hypotonia. The cataplectic episodes precipitated by emotional stimuli is a relatively late phenomenon. The cataplectic falls are often diagnosed as seizures or syncope as these are better known diseases compared to the former. Atonic, astatic and myoclonic seizures are common in children and can exactly resemble cataplexy and only a careful history can differentiate between them. Cataplexy is a feature in 60-100% cases of childhood narcolepsy but as the first manifestation is observed only in 10% of them.[28] The symptoms are mostly negative, sagging of jaw and buckling of knees being the most common but positive phenomena like facial twitching and even urinary incontinence can occur rarely. The usual precipitant is a positive emotion like laughter and joy but negative emotions like anger and interestingly even tickling can cause cataplexy. Negative emotion may sometimes result in cataplexy-like episodes like knee buckling in some normal subjects. Oculobuccofacial musculature involvement is more common in children. Literature also describes typical facies characterized by repeated opening of mouth, protrusion of tongue and ptosis which interestingly responds to medical treatment. The presence of this facial phenotype along with recurrent falls and fatiguability may lead to the wrong diagnosis of neuromuscular diseases like myasthenia. Finally cataplectic falls in children may not be precipitated by laughter or other emotions. Hallucinations which often generate fear and leads to sleep problems in children usually result in psychiatric consultations or a visit to the faith healer. However, the clinical and polysomnographic traits of this disorder does not differ from that of the adult counterpart. Costa el reported no deviation from the classic presentation in their 5 Portugues boys with narcolepsy aged between 6 and 10 years. It is interesting to note that all of them tested positive for HLA...and displayed SOREMPs on MSLT. Hypocretin level was low in the CSF of one of their subjects in whom lumbar puncture could be performed. Obesity was the single most important association with 4/5 having a BMI>75th percentile while history of influenza vaccination and affected family member were obtained in only one subject each. There are no definite clinical markers to distinguish between primary and secondary cases of narcolepsy although some reports suggest that early and frequent episodes of cataplexy is a pointer to the latter.

Hallucinations are reported by more than half of patients. They are experienced especially during transition from wakefulness to sleep although daytime hallucinations can occur occasionally.

The description of these experiences by patient may vary with some of them having vivid dreams to others having a multisensory perception of formed images, sounds and touch. Visual hallucinations can also have a elementary of a formed character although the former is common. Cenesthetic experiences (rubbing, picking and light touching) are very characteristic. The auditory hallucinations can be in the form of vague sounds, sentences, instructions or even have a song like character which can be difficult to differentiate from that of schizophrenia. A careful search for the other cardinal symptoms and a psychiatric consultation has to be sought in such situation. In the pediatric population, the history may not be productive in terms of the nature of hallucinations, as children may either consider these experiences as real or be frightened by them or may not even recollect them.

It is important to clinically differentiate narcolepsy patients from those with hypersomnolence. The irresistibility to sleep and refreshed feeling after sleep are characteristic of patients with narcolepsy. Patients with narcolepsy feels refreshed after short naps and after nighttime sleep and find no difficulty whatsoever in starting off his day.[33] On the contrary, patients with idiopathic hypersomnia have persistent sleepiness not relieved by naps or nocturnal sleep and find it difficult to catch up with the day. Use of a formal questionnaire as part of sleep evaluation can further improved the odds of diagnosis, the most widely used ones being the Swiss Narcolepsy scale and Ullanlinna Narcolepsy Score (UNS). Both are sensitive instruments with more than 95% sensitivity while the former has a better specificity in the diagnosis of confirmed narcolepsy.[34]

Hublin etl has developed a 11- item questionnaire called Ullanlinna Narcolepsy Scale (UNS encompassing both decreased latency and increased urge to sleep (7 items) as well as symptoms suggestive of narcolepsy (4 items). The patients receive a score ranging from 0-44 and a score> 14 can identify patients with narcolepsy with a sensitivity of almost 100%.The SNS uses a five pointed weighted scale where the patient is interviewed on whether or not they have an inability to fall asleep, feeling bad or unrefreshed in the morning, tendency for a day time nap and if they have any symptoms suggestive of cataplexy(buckling of knees, sagging of jaw).The instrument uses both positive and negative values and a seemingly complex assessment to diagnose narcolepsy.[34]Despite availability of these scoring measure, the diagnostic challenge still remains considering mono-symptomatic presentations ,comorbid sleep disorders, systemic associations like obesity and precocious puberty as well as the myriad of manifestation and associations seen in patients especially those of the pediatric age group

Another important aspect to discuss in this context is the value of the various investigative parameters used in the diagnostic work up and confirmation of narcolepsy and the internal correlation between them. Based on the ICSD-2 criteria, Narcolepsy is a clinical diagnosis which is confirmed by the presence of ≥ 2 SOREMPS and a mean sleep latency ≤ 8 minutes on a standard 4-5 nap multiple sleep latency test (MSLT). In this

test, patient is given 4-5 opportunities of 20 minutes each to sleep at 2-hour intervals starting 1.5 hour after waking up. The criteria for diagnosis are applicable both for both adults and children. MSLT apart from confirming the diagnosis also aids in quantifying the excessive daytime sleepiness as measured by the sleep onset latency. Mean wakefulness time estimated by asking the patient to stay awake during the stipulated period of 40 minutes is also used albeit sparingly to assess the severity of disease and response to treatment. A systematic historical evaluation for sleep disorders supported by overnight PSG is essential to exclude important differentials like sleep apnea, restless leg syndrome, circadian rhythm disturbance and idiopathic hypersomnia. Polysomnography also helps us to assess the quality of night sleep which we know is significantly affected in many patients. Narcolepsy with cataplexy is more often associated with HLADQB1*0602 positivity and reduced levels of CSF hypocretin (>90%). Those with reduced hypocretin are more likely to be HLA DQB1*0602 positive. Only about half of those with narcolepsy without cataplexy have these laboratory abnormalities. Undetectable or low hypocretin level <110 pg/dL is virtually diagnostic of narcolepsy with cataplexy. There is insufficient information from medical literature to make a comparative assessment of these abnormalities among adult and pediatric patients. Nevertheless, it is well established that children and adolescents with narcolepsy also do show HLA positivity and low hypocretin subjects.

An important diagnostic hurdle that remains is of associated sleep comorbidities. Narcolepsy may be overlooked in the presence of other sleep disorders and vice versa owing to the high incidence of their coexistence. The most common sleep abnormality outside the spectrum of narcoleptic semiology observed in these patients is motor abnormalities during sleep. A recent study found that 75% patients had periodic limb movement index (PLMI>5) and 20% of them fulfilled criteria for restless leg syndrome (RLS). The spectrum of sleep disorders includes obstructive sleep apnea, insomnia, parasomnia, and bruxism. The high incidence of sleep apnea may be secondary to increased risk of obesity.

Management

It cannot be overemphasized that education of the patient and family is the cornerstone of narcolepsy management. Along with the judicious use of various pharmaceutic agents this can transform the lives of its victims. With children, counseling of parents and teachers as well as other caregivers is extremely important. Children with narcolepsy may suffer from low self-esteem because of poor academic performance, stigma, and behavioral problems. They may be disinclined to actively socialize or engage in outdoor sport. So, the physical, socio-cultural, and academic impediments should be addressed separately in a constructive manner by a multi-disciplinary team.

Patients should also be screened for depression, anxiety and other sleep disorders like sleep apnea or restless leg syndrome. Scheduled naps of 15 minutes two times in a day along with regular nighttime sleep timing and duration can alleviate symptoms in moderate to severely sleepy children with narcolepsy.

All the three wake promoting agents namely methylphenidate (10-40 mg/d), modafinil/armodafinil (50-400 mg/d) and dextroamphetamine (5-40 mg/d) can be safely used in children. However, the first two agents can cause neuropsychiatric side effects like nervousness, irritability, and insomnia. Gastrointestinal side effects can rarely be dose limiting in patients receiving modafinil. Pemoline and seligiline are less often used because of risk of toxicity. Pitolisant is an H3 receptor blocker which has been showed in clinical trials to reduce daytime sleepiness as documented by reduction in ESS of four points. The baseline sleepiness was still significantly higher than normal in treated subjects with a modest disruption of nocturnal sleep. Solriamfetol is a new selective reuptake inhibitor of norepinephrine and dopamine which is being investigated as a wake promoting agent in narcolepsy.

Cataplexy in children is also treated in a similar fashion to that of adults with SSRIs and sodium oxybutate. Sodium oxybate is a sodium salt of gamma hydroxy butyric acid which has a multi-pronged utility in the treatment of narcolepsy. At doses of 4.5-9 mg sodium oxybate not only suppresses cataplectic attacks, but also reduces daytime sleepiness, improves nighttime sleep with less number of awakenings and arousals as well as patient reported sleep quality. It also increases time spent in stage 3 NREM sleep without affecting REM sleep.

With more and more evidence accumulating in favour of the autoimmune roots of this rather focal disease of the brain in terms of anatomical substrates involved, it augers well to emphasize the importance of initiating or at least considering the option of immunomodulation in cases refractory to standard line of management. The only study which has addressed the potential benefits of immunotherapy is an observational case control study where 29 of the 59 children received three doses of monthly infusions of 1g/kg intravenous gamma globulin. There was no significant impact observed by the authors in terms of severity of symptoms or achievement of desired therapeutic targets. This solitary observation is clearly insufficient to make any assumptions on the future scope of immunotherapy given the wide array of immunomodulatory agents that are available and the improvements in patient selection that can be achieved with the help of clinical, laboratory and genetic data.

Genetic transfer of orexin into the zona incerta, dorsolateral pons and amygdala neurons have been attempted in animal models with reasonable success especially in suppression of cataplexy. Now with a firm understanding of the role of orexin in modulating the brain circuits responsible for sleep wake maintenance and its deficiency being identified as the central mechanism of narcolepsy-cataplexy, gene transfer and cell transplantation to abate or circumvent this would be an important avenue for therapeutic research in the recent future.

A practical algorithm for the management was proposed by the authors in a previous publication for diagnosis and management of narcolepsy.

REFERENCES

1. Scammell TE. Narcolepsy. New England J Med. 2015; 373: 2654-2662.
2. Longstreth Jr WT, Koepsell TD, Ton TG, Hendrickson AF, Van Belle G. The epidemiology of narcolepsy. Sleep. 2007; 30: 13-26.
3. Wijnans L, Lecomte C, de Vries C, Weibel D, Sammon C, Hviid A, Svanström H, Mølgaard-Nielsen D, Heijbel H, Dahlström LA, Hallgren J. The incidence of narcolepsy in Europe: before, during, and after the influenza A (H1N1) pdm09 pandemic and vaccination campaigns. Vaccine. 2013; 318: 1246-1254.
4. Dauvilliers Y, Arnulf I, Lecendreux M, Monaca Charley C, Franco P, Drouot X, d'Ortho MP, Launois S, Lignot S, Bourgin P, Nogues B. Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France. Brain. 2013; 136: 2486-2496.
5. Mignot E, Hayduk R, Black J, Grumet FC, Guilleminault C. HLA DQB1* 0602 is associated with cataplexy in 509 narcoleptic patients. Sleep. 1997; 20: 1012-1020.
6. Nishino S, Okura M, Mignot E. Narcolepsy: genetic predisposition and neuropharmacological mechanisms. Sleep medicine reviews. 2000; 4: 57-99.
7. Mignot E, Lammers GJ, Ripley B, Okun M, Nevsimalova S, Overeem S, Vankova J, Black J, Harsh J, Bassetti C, Schrader H. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Archives of neurology. 2002 ; 59: 1553-1562.
8. Burgess CR, Scammell TE. Narcolepsy: neural mechanisms of sleepiness and cataplexy. J Neurosci. 2012; 32: 12305-12311.
9. Sakurai T. Orexin deficiency and narcolepsy. Curr Opin Neurobiol. 2013; 23: 760-766.
10. Peyron C, Tighe DK, Van Den Pol AN, De Lecea L, Heller HC, Sutcliffe JG, Kilduff TS. Neurons containing hypocretin (orexin) project to multiple neuronal systems. J Neurosci. 1998; 18: 9996-10015.
11. Hong SB, Tae WS, Joo EY. Cerebral perfusion changes during cataplexy in narcolepsy patients. Neurology. 2006 ;66:1747-1749.
12. Dauvilliers Y, Comte F, Bayard S, Carlander B, Zanca M, Touchon J. A brain PET study in patients with narcolepsy–cataplexy. J Neurol Neurosurg Psychiatryy. 2010; 81: 344-348.

13. Cvetkovic-Lopes V, Bayer L, Dorsaz S, Maret S, Pradervand S, Dauvilliers Y, Lecendreux M, Lammers GJ, Donjacour CE, Du Pasquier RA, Pfister C. Elevated Tribbles homolog 2–specific antibody levels in narcolepsy patients. J Clin Invest. 2010; 120: 713-719.
14. Kawashima M, Lin L, Tanaka S, Jennum P, Knudsen S, Nevsimalova S, Plazzi G, Mignot E. Anti-Tribbles homolog 2 (TRIB2) autoantibodies in narcolepsy are associated with recent onset of cataplexy. Sleep. 2010 ; 33: 869-874.
15. Longstreth Jr WT, Ton TG, Koepsell TD. Narcolepsy and streptococcal infections. Sleep. 2009 ; 32: 1548.