Original Article

Central Disorders of Hypersomnolence in Children and Adults: A Comparative Study from South India

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Abstract

Background: Narcolepsy and idiopathic hypersomnolence (IHS) are rare disorders. In Western populations, the reported prevalence of narcolepsy is 0.02%–0.05%. In Indian subcontinent, there are few reports on narcolepsy and none on IHS so far. Here, we compared the clinical and polysomnographic profile of narcolepsy/IHS among the pediatric and adult groups. **Materials and Methods:** The patients presenting with excessive daytime sleepiness (EDS) attending sleep clinic from January 2010 to December 2015 were included. Patients were diagnosed with narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and IHS based on the International Classification for Sleep Disorders criteria. Patients with secondary causes of EDS were excluded from the study. **Results:** A total of 56 patients were included in the study (29 males and 27 females). The mean age of symptom onset was 29 years (males – 34 years and females – 24 years). Twelve (21%) patients had NT1, five (9%) patients had NT2, whereas 38 (68%) patients had IHS compared to narcolepsy, the IHS had an older mean age at presentation. The average time from symptom onset to diagnosis was 71 months. Classical tetrad of narcolepsy was rarely found in pediatric cohort, but they had more behavioral problems and weight gain. Pediatric cohort of IHS also reported behavioral problems. The mean sleep-onset latency was 3.1 min, while the mean rapid eye movement latency was 7.2 min. **Conclusion:** The pediatric narcolepsy patients tend to have less classical symptoms and more behavioral/eating problems as compared to adult cohort. There is significant delay in diagnosing narcolepsy, indicating the need to increase awareness among the physicians about this rare treatable disorder.

Keywords: Idiopathic hypersomnolence, multiple sleep latency test, narcolepsy, pediatric, polysomnography

Introduction

The idiopathic central disorders of hypersomnolence including narcolepsy and idiopathic hypersomnolence (IHS) are characterized by excessive daytime sleepiness, despite having normal quality and duration of nocturnal sleep. According to the International Classification for Sleep Disorders (ICSD-3) criteria,[1] both have been categorized under central disorders of hypersomnolence along with other secondary disorders such as hypersomnia due to a medical disorder, medication or substance use associated with a psychiatric disorder, as well as insufficient sleep syndrome. An extremely rare disorder with a reported prevalence of <0.05% in Europe and North America, the narcolepsy is often misdiagnosed for years. Many authors have found that even though mostly reported in middle adulthood, symptoms can often be traced to childhood or adolescence years.[2] With increased availability of human leukocytic antigen (HLA) analysis and cerebrospinal fluid (CSF) hypocretin assay, more patients are receiving the diagnosis of narcolepsy or IHS; however, many centers still depend on polysomnography (PSG), which is the gold standard for establishing a diagnosis, after excluding secondary causes.

Most of the reports of central hypersomnolence in literature are from Europe and North America, of mostly Caucasian cohorts. There are a few reports from Asia and India on this rare condition, especially narcolepsy with some showing a link with viral infections H1N1 as well.[3] Reports from India on this rare condition are limited to a few small series and case reports[4-8] and none have reported on IHS as well.

Aim of the study

This study aimed to look at the clinical and polysomnographic profile of a cohort of patients with central hypersomnolence narcolepsy and IHS from a single center. In addition, we attempted to identify the similarities and differences between the adult and pediatric (<18 years) patients with narcolepsy/IHS.

Materials and Methods

The study was conducted at Comprehensive Center for Sleep Disorders, under the Department of Neurology,

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Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India. Ours is a tertiary care center for neurological and cardiovascular disorders, catering to an average of 200 new and 400 review patients annually, from mostly two states of South India. All consecutive patients attending neurology/sleep clinic with symptoms of excessive daytime sleepiness (EDS), where secondary causes such as obstructive sleep apnea (OSA), periodic limb movement disorders, and medication-related conditions have been ruled out by a history and relevant investigations and a diagnosis of narcolepsy/IHS has been made were prospectively recruited for the study after informed consent. We did not include Kleine–Levin syndrome in our study group. Recruitment period was from January 2010 to December 2015 (6 years). The conduct of the study was approved by the Institutional Ethics Committee. Their demographic details, clinical profile, mean duration of symptoms before diagnosis, and referral/initial diagnosis made before arriving here were extracted into a structured pro forma through interview by two of the study neurologists (M.T. and S.E.S.). The patients with suspected central hypersomnolence were asked to refrain from any hypnotics/antidepressants and maintain a 2-week sleep log before attending the laboratory for sleep study. A total of 11 of our patients were given a clinical diagnosis of probable narcolepsy from outside and were on medications also. We asked them to stop the medicines for 2 weeks before the sleep study. All the patients' PSG and multiple sleep latency test (MSLT) on the consecutive day were performed by two of our neurotechnologists (S.N.N. and A.C.A.), with experience in performing the sleep studies since 2009. All the studies were reviewed by two of the neurologists, with experience in interpreting the sleep studies (S.E.S. and A.L.R.). Details extracted included night sleep parameters such as sleep-onset latency, sleep efficiency, arousal index, fraction of total sleep time spend in nonrapid eye movement stages 2 and 3, and rapid eye movement (REM) sleep, REM latency, and any periodic leg movements, or respiratory events. Those patients with moderate-to-severe OSA and periodic limb movement disorders were excluded from the study. The patients whose overnight PSG was essentially normal with a good sleep efficiency of >85% were subjected to MSLT. The parameters looked into were median sleep-onset latency, presence or absence, and number of sleep-onset REM periods (SOREMPs) and REM-onset latency.

Narcolepsy was diagnosed as per the ICSD-3 symptoms of EDS and MSLT showing reduced sleep-onset latency <8 min with two or more SOREMPs out of the five naps.[1] Patients with symptoms of EDS, with short sleep-onset latency of ≤8 min, with no or one SOREMPs were grouped as IHS. We did not perform CSF hypocretin assay or HLA typing for patients included in the study.

We compared the clinical and polysomnographic profile of patients with narcolepsy and IHS across the two age groups <18 versus ≥18 years. Statistical analysis was performed using SPSS Version 18 Software (SPSS Inc, Chicago, IL). Baseline data were expressed in means and percentages. Chi-square test was used to test the association between the variables with $P < 0.05$ considered as statistically significant.

Ethical approval

The study was performed in accordance with the ethical standards of the Institutional Ethics Committee (IEC – Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum), and with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained for all data collected from the participants.

Results

Demography

Of the 1200 new patients referred to sleep clinic during the study period, our major diagnosis was OSA (70%), followed by insomnia (12%). A total of 56 patients (4.6%) satisfied the criteria for a diagnosis of central disorder of hypersomnolence. Baseline data are given in Table 1.

There was a statistically significant difference in the age of presentation between the narcolepsy and IHS group ($P = 0.0003$), with narcolepsy types 1 and 2 presenting at a younger age group.

Mean duration of symptom onset to presentation/diagnosis to sleep clinic was 5.8 years (70.5 months), 72.68 months for IHS, and 86.56 months for narcolepsy, which was comparable between the two groups. However, we found a significant difference in the diagnostic delay, with an average of 2.2 years for younger patients and 8 years for the older patients.

Among the narcolepsy patients, 14 were 18 years old and above (58.3%), whereas 10 were below 18 years (41.7%). We further compared the two subpopulations. In the younger subgroup of below 18 years, the mean age was 13.3 years, with seven females and three males. In the 18 years and above subgroup, the mean age was 36 years, with nine females and five males.

Referral patterns

Most of the patients (21 patients, 37.5%) were referred by the physicians and neurologists (20 patients, 35.7%). The most common initial referral diagnosis was hypersomnolence disorder (narcolepsy or idiopathic; 35 patients, 62.5%), out of which, 14 were eventually diagnosed as narcolepsy. Seizures/loss of consciousness and OBA/snoring were the second most common referral diagnoses (four patients each), followed by disturbed night sleep (3) and headache/migraine (2). Among the narcolepsy subgroup, highest referral was from neurologists (11), followed by physicians (7) and psychiatrist (4).

Symptoms

All the 56 patients had EDS (100%). Comparison of other symptoms between narcolepsy and IHS is given in Table 1. Nineteen patients of narcolepsy had cataplexy (33.9%) that was used for classification. Symptoms comparison between the NT1 and NT2 are given in Table 2 and comparison

between the pediatric and adult narcolepsy is given in Table 3. We assessed behavioral/psychiatric symptoms in our patients with the help of a psychiatrist and found that increased anger was the most common symptom (10/16), followed by mood changes in 4/16 patients. About two of our patients had psychotic symptoms at presentation. We had a daytime sleepiness quantified by Epworth Sleepiness Scale in only 30 of our adult patients who had a mean ESS score of 15.8.

Polysomnography and multiple sleep latency test finding

The PSG data were available for all 56 patients. The findings are summarized in Table 4. Overnight PSG showed the mean sleep efficiency of 88.02%, with a mean slow-wave sleep-onset latency of 24.82 min, and mean REM-onset latency was 112.18 min. There was no significant difference noted among the narcolepsy and IHS group on comparing these parameters. The MSLT data of the whole group showed a mean sleep-onset latency of 187.1 s. The mean sleep-onset latency for narcolepsy patients was 1.8 ± 1.7 min and that for IHS patients was 4.1 ± 2.0 min, difference being statistically significant ($P < 0.0001$). The mean REM-onset latency during the MSLT was 7.20 min with much shorter latency in narcolepsy subgroup as compared to IHS (5.3 ± 5.5 min for narcolepsy patients and 12.7 ± 4.4 min for IHS patients; $P < 0.0072$). Among the IHS group, nine had one SOREM and the rest had no REM recorded in their naps. PSG and MSLT parameters did not differ significantly across the adult and pediatric populations.

Table 1: Baseline characteristics of the cohort

	NT-1 and NT-2	IHS	*P*
n	24 (19 and 5)	32	
Male:female	8:16	21:11	NS
Mean age of symptom onset	Male 20.9 years	Males 37.95 years	0.003
	Female 19.75 years	Females 30.82	
Mean age of diagnosis	26.6 years	35.5 years	
Delay in diagnosis	86.58 months	72.68 months	NS
Symptoms			
EDS	24	32	
Cataplexy	19	0	
Hypnagogic hallucinations	12	0	
Sleep paralysis	7	2	
Behavioral/psychiatric symptoms	16	9	
Weight gain	7	2	

EDS=Excessive daytime sleepiness, IHS=Idiopathic hypersomnolence, NS=Nonsignificant, NT-1=Narcolepsy type 1, NT-2=Narcolepsy type 2

Table 2: Comparison between narcolepsy type 1 and narcolepsy type 2

	NT-1	NT-2
n	19	5
Male:female	13:6	1:4
Mean age of symptom onset (years)	22	14
Mean age of diagnosis (years)	28	20
Symptoms (%)		
EDS	19 (100)	5 (100)
Cataplexy	19 (100)	0
Hypnagogic hallucinations	12 (63.2)	0
Sleep paralysis	7 (36.8)	0
Behavioral/psychiatric symptoms	15 (78.9)	1 (20)
Weight gain	5 (26.3)	2 (40)

EDS=Excessive daytime sleepiness, NT-1=Narcolepsy type 1, NT-2=Narcolepsy type 2

Discussion

Disorders of central hypersomnolence, including narcolepsy and IHS, being rare often go undiagnosed and underreported, especially from India. One questionnaire-based study on sleep disorders from South India reported the symptoms suggestive of narcolepsy in a little over 1% of respondents, indicating that this condition may not be extremely rare.[9] Our series, with 56 patients (24 with narcolepsy) represent the largest series of central hypersomnolence reported from India so far in the literature. We could come across only a few case reports and two small series of narcolepsy[4-8,10] and none with IHS in the existing literature from India.

Table 3: Comparison between pediatric and adult narcolepsy

	<18 years (*n*=10), *n* (%)	>18 years (*n*=14), *n* (%)	*P*
EDS	10/10	14/14	
Cataplexy	9/10 (90)	10/14 (71.4)	
Sleep paralysis	1 (10)	6 (42.8)	
Hypnagogic hallucinations	7 (70)	5 (35.7)	
Tetrad positive	1/10	5/14	
Nightmare	6 (60)	9 (64.28)	
Cognitive/scholastic decline	5 (50)	1 (0.07)	
Weight gain	5 (50)	0	
Behavioral change	6 (60)	10 (71.4)	
Delay in diagnosis (years)	2.2	8	0.001

EDS=Excessive daytime sleepiness

Table 4: Polysomnography and multiple sleep latency test findings in narcolepsy and idiopathic hypersomnolence

	Narcolepsy 1 and 2	IHS	*P*
Overnight PSG			
Sleep efficiency	89.01%	87%	NS
Slow-wave sleep latency	20.2 min	28.23 min	
REM latency	100 min	134.3 min	
MSLT			
Mean sleep-onset latency	1.8±1.7 min	4.1±2 min	<0.0001
Mean REM-onset latency	5.5±5.3 min	12.7±4.4 min	<0.0072

PSG=Polysomnography, REM=Rapid eye movement, MSLT=Multiple sleep latency test, IHS=Idiopathic hypersomnolence

Male preponderance in narcolepsy and IHS has been universally reported in almost all series[11-13] including those from Asia[14,15] and India as well. However, ours was a female-predominant cohort, in both narcolepsy and IHS with the pattern observed in younger and older population as well. Such an observation has rarely been reported in small, single institutional series[16-18] in both narcolepsy and IHS. Whether this observed difference is due to referral and reporting bias inherent to single institutional studies or due to a genuine difference in gender predilection in South Indian population needs further clarification with larger multicenter and population-based studies.

Narcolepsy usually starts in the second decade of life. In a study from Olmsted County, the median age of onset was 16 years,[11] while that from Czech Republic was 18 years.[19] There is a bimodal age distribution described, with a large peak around 15 years of age and a smaller peak around 36 years of age.[20] The previous authors from India have also reported a mean age of onset in the early 20s, which is comparable to our cohort of narcolepsy.[8,10] We found a significant difference in the age of symptom onset between the two groups with IHS cohort having a later onset of symptoms. Reviews on IHS have shown a wide range of symptom onset from late teens to mid-30s.[21] A large series from the United Kingdom[13] showed a younger age of onset (mean = 16.6 years), while the diagnosis was made around one and a half decades later in the 30s. Whether the later presentation in our IHS cohort is due to delay in diagnosis needs to be studied further as milder degrees of sleepiness in the adolescent and younger ages manifesting as napping in the classes are often ignored, unless it starts affecting them scholastically or at job, which rarely happens in IHS. Furthermore, we do not have any Indian case on the same to compare with.

Delay in diagnosis of narcolepsy is reported as early as 1976 with 5 years reported as an average time elapsed between symptom onset and correct diagnosis.[22] A United Kingdom-based study found that even though 66% of patients received their diagnosis within 5 years, around 24% had a delay (>10 years) in arriving at the diagnosis.[23] The median delay in diagnosis ranges from 8.4 years[24] to 22.1 years.[25] Even though delay in diagnosis is reported across the world, a shortening of delay in the most recent decade of symptom onset has been observed by some authors.[26] Our cohort had an average diagnostic delay close to 5 years, compared to other Indian studies. Most of our patients were referred by the physicians or neurologists with a suspicion of narcolepsy.

Analyzing symptoms in narcolepsy and IHS, we found that other than daytime sleepiness, other symptoms are rarely seen in IHS. This is in line with previous reports on IHS.[13,16] In a cohort of 77 patients, Anderson *et al*. reported that other than vivid dreams in a quarter of patients, other symptoms such as hypnagogic hallucinations and sleep paralysis are rarely seen. A Norwegian study comparing symptom profile of central hypersomnolence with CSF hypocretin-1 levels found that hypnagogic hallucinations and sleep paralysis are often seen in narcolepsy type 1 (NT1) and have a lower but comparable prevalence in NT2 and IHS. We found a few patients with IHS presenting with behavioral symptoms, which are underreported in literature.

In narcolepsy, even though core symptoms of pediatric patients are similar to adult patients, their expression differs as reported by various authors. In a review on childhood narcolepsy,[2] the author reported that besides classical symptoms of narcolepsy, others such as nocturnal bulimia, obesity, decline in school performance, and behavioral/emotional problems were usually seen in children than adults. Cataplectic attacks are often mistaken as falls or atonic seizures and wrongly treated with antiepileptics as was seen in our pediatric cohort too. While some authors found no significant difference between the classical symptom prevalence in adult and pediatric narcolepsy,[20] some noted that hypnagogic hallucinations and nightmares are more common in pediatric patients and sleep paralysis is less frequently seen, which was comparable with our observation as well.[2] We found more weight gain and personality/behavioral disorders in our pediatric narcolepsy patients, similar to reports from Asia and Europe.[27,28] Furthermore, high levels of attention-deficit hyperactivity disorder have been reported by French authors.[29] However, we could not find precocious puberty in our patients.

Polysomnography and multiple sleep latency test finding

The previous studies[30] have shown that the number of SOREMPs decreases as a function of age and the mean MSLT increases with age. This was also observed in our cohort. An interesting finding in our patients was that although the recent ICSD-3 criteria requires the presence of ≥2 SOREPMs as well as MSLT of <8 min to categorize a patient as NT1 even in the presence of cataplexy, we had seven patients (out of 24), that is, 29.1% who had EDS and cataplexy but the number of SOREMPs were <2. We included these cases in NT1 group as they had a clear history suggestive of cataplexy. It is possible that the stringent requirement of ICSD-3 criteria of two or more SOREMPs might miss the diagnosis in such cases. This has been highlighted in the Dauvilliers study, where only 84.2% of cases of narcoleptics (diagnosed on the basis of unequivocal cataplectic attacks and HLA positivity) had two or more SOREMPs, whereas the rest 15.8% had <2 SOREMPs. Again out of the seven patients with <2 SOREMPs, two were below 18 and five were 18 years and above, further supporting the fact that the sensitivity of current criteria for narcolepsy decreases with age as the number of SOREMPs decrease. However, our study was not supported by HLA or CSF hypocretin analysis and further large-population studies are needed to elucidate the same.

Our observational study constituting the largest cohort of central hypersomnolence from India is not without its limitations. We made the diagnosis based on clinical and electrophysiological criteria after excluding the secondary causes but could not perform the HLA study or CSF hypocretin levels due to lack of resources. Furthermore, we did not quantify excessive daytime sleepiness in our study cohort as Epworth Sleepiness Scale was not available for all the patients, especially in

the pediatric cohort. This made it difficult to analyze the treatment response in the current cohort. Furthermore, a single institutional study may not be truly reflective of the clinical profile of rare diseases.

Concluding,observations from our cohort throws insights into disorders of central hypersomnolence ,which often remains underdiagnosed. Our cohort had a significant delay before arriving at the diagnosis; however, many were referred to us with a clinical suspicion of narcolepsy itself. Ours was a female-predominant cohort, unlike the previous reports of male preponderance of narcolepsy in literature. IHS showed more behavioral or personality problems that have not been reported in the literature. Pediatric and adult narcolepsy did not significantly differ in their core symptoms, except for weight gain and behavioral issues that were more in the pediatric cohort. Epidemiological studies on rare diseases such as narcolepsy are difficult to perform in resource-poor countries. Hence, we are planning to establish a narcolepsy database linking other neurology centers in our state, whereby we can generate more clinical information about this rare disease and plan genetic studies as well.

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Conflicts of interest

There are no conflicts of interest.

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