A four year experience in narcolepsy from a sleep clinic at a tertiary care centre with a short review of contemporary Indian literature

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Narcolepsy is a common sleep disorder in Western countries but rarely reported from India. Here, we report a small case series of four narcolepsy patients seen over a four year period in the sleep clinic of a tertiary care hospital in north India. The diagnosis was established by clinical history and two or more sleep-onset rapid eye movements (SOREMs) on multiple sleep latency tests (MSLTs) following overnight polysomnography (PSG). The mean age of patients was 26.2±6.4 yr; one patient had associated cataplexy and another one had all four cardinal symptoms of narcolepsy. All these patients had a history of excessive daytime sleepiness (EDS). The mean body mass index was 24.2±4.7 kg/m². The mean sleep latency during MSLT was 2.7±1.3 min, and the mean REM latency was 5.7±2.9 min. Narcolepsy, although rarely reported from India, should be suspected in young non-obese patients complaining of EDS and confirmed by performing MSLT following overnight PSG.

Narcolepsy is a sleep disorder characterized by a tetrad of excessive daytime sleepiness (EDS) in the form of sleep attacks, cataplexy, hypnagogic hallucinations and sleep paralysis[1]. Pathogenesis of the disease is linked to the loss of neuropeptides, orexin-A and orexin-B secreted from neurons in the lateral hypothalamus. Narcolepsy is of two types, NT1 and NT2, depending on the presence and absence of cataplexy, respectively. NT1 is associated with reduced cerebrospinal fluid (CSF) orexin-A levels, whereas the levels are normal in NT2. The latter shares similar clinical features with NT1, but its pathogenesis is still unknown. Secondary narcolepsy occurs in diseases affecting midbrain or posterior hypothalamus such as stroke, tumours or trauma. The global prevalence of NT1 is 25-50 and that of NT2 is 20-34/ 100,000 individuals[2,3]. In European, North American and Asian populations, the prevalence of narcolepsy is about 30 cases/ 100,000 individuals. The prevalence of narcolepsy varies among different ethnic populations[3]. In Japanese population, the prevalence of narcolepsy is 160 cases/ 100,000, highest in the world, whereas in Jewish and Saudi Arabian populations, the prevalence is 10/ 100,000 individuals[3]. These differences in the prevalence of narcolepsy among different ethnic populations

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can be attributed to genetic and environmental risk factors. Human leucocyte antigen HLA-DQB1*0602 is the main allele associated with narcolepsy. Depending on the population, 86-98 per cent of patients with NT1 carry the HLA-DQB1*0602 alleles. Other HLA alleles such as HLA-DQB1*0301, HLA-DPB1*0501, HLA-A*1101, HLA-B*3501, HLA-B*5101 and HLA-C*0401 can also predispose individuals to narcolepsy, but to a lesser extent[3]. It has also been reported that H1N1 influenza A virus infection is associated with an increased prevalence of narcolepsy. Besides influenza virus infection, *Streptococcus pyogenes* can also trigger NT1[3]. From the Indian subcontinent, only a few published case reports of narcolepsy are available[4-9]. The prevalence of narcolepsy may be genuinely lower in India; however, due to lack of awareness and laboratory facilities, underdiagnosis of narcolepsy cannot be ruled out.

The present study describes four confirmed patients with narcolepsy seen over a four year period (March 2012-December 2015) who fulfilled the International Classification of Sleep Disorders diagnostic criteria for narcolepsy[10]. Patients having a history of EDS at least for three months, mean sleep latency of less than or equal to eight minutes and two or more sleep-onset rapid eye movements (SOREMs), *i.e.* REM sleep occurring within 15 min of sleep onset, were included. Patients having other sleep disorders such as obstructive sleep apnoea (OSA), central sleep apnoea, periodic limb movement disorder, sleep deprivation circadian rhythm sleep-wake disorders, idiopathic hypersomnia and history of substance abuse were excluded. The study was conducted amongst the patients attending the Sleep Clinic of the department of Internal Medicine, All India Institute of Medical Sciences (AIIMS), New Delhi, India. The sleep clinic registry was accessed to identify all the patients suffering from narcolepsy. Polysomnography (PSG) was conducted in the Sleep Laboratory of the department of Internal Medicine, AIIMS, on SOMNOscreen™ plus PSGmachine (SOMNOmedics, Germany) as described previously[11]. The PSG data were scored manually. American Association of Sleep Medicine (AASM)-2012 guidelines were used for scoring the apnoeic and hypopnoeic events[12], and the multiple sleep latency test (MSLT) was performed according to the AASM Task Force Recommendations[13]. None of the patients were on any central nervous system stimulants or depressants or any drugs that could alter the REM sleep. All clinical, PSG and MSLT data were entered in Microsoft® Excel Spread sheet, and descriptive statistics were used for analysis. The study was approved by the Institutional Ethics Committee.

Of the 1175 patients seen at the sleep clinic during the study period, four patients were diagnosed with narcolepsy. All diagnosed patients were males, and the mean age of onset of narcolepsy symptoms was 26.2±6.4 yr. One patient was excluded because of concomitant severe OSA. One patient with narcolepsy had cataplexy and another one presented with all the four cardinal symptoms of narcolepsy. Table I provides PSG and MSLT data of these patients. All patients showed short sleep latencies with an average of 2.7±1.3 min and two or more SOREMs on MSLT. The mean Epworth Sleepiness Score was 13±6.8. The Indian literature available on narcolepsy was also reviewed. Comparison of the details of 28 narcolepsy cases reported (including the current study) from India[4-8] is given in Table II.

The mean age of onset (third decade) of narcolepsy in the present study was similar to the previously

Table I. Polysomnography and multiple sleep latency test data of four patients with narcolepsy

Parameters	Values
Total sleep time (min)	461.7±47.5
Sleep efficiency (%)	92±4.9
REM (%)	17.8±5.2
NREM 1 (%)	7.13±2.2
NREM 2 (%)	44.8±8.5
NREM 3 (%)	30.2±4.3
AHI (events/h)*	1.35 (0.1-8.4)
Baseline SpO_2 (%)	96.75±0.9
Minimum saturation (%)	89.25±7.8
Δ SpO_2 (%)*	4.5 (3-15)
Desaturation Index (events/h)*	0.95 (0.1-8.1)
Total Arousal Index (events/h)*	38.5 (14.5-61.9)
Respiratory arousal index (events/h)*	0.15 (0.02-5.4)
Mean sleep latency (min)	2.7±1.3
REM latency (min)	5.7±2.9

Data are expressed as mean±SD; *Data are provided in median (interquartile range). REM, rapid eye movement; NREM, non-rapid eye movement sleep; AHI, apnoea-hypopnoea index (events/h); SpO_2, Oxygen Saturation Targeting by Pulse Oximetry; Δ SpO_2, difference between baseline SpO_2 and minimum SpO_2; SD, standard deviation

Table II. Summary of various reported Indian studies

A. Clinical parameters of 28 narcolepsy patients

Author	Type of study	Frequency (%)	Age onset (yr)	BMI (kg/m²)	Type	EDS	Cataplexy (%)	Hypnagogic hallucinations (%)	Sleep paralysis (%)	Sleep attacks
Gupta et al[4] (n=20)	Observational	20/1024 (1.9)	25±10	26±4	Idiopathic	All	12/20 (60)	8/20 (40)	12/20 (60)	All
Bhatia and Arif[5] (n=1)	Case report	NA	NA	26.5	Idiopathic	Yes	Yes	No	No	Yes
Shehna et al[6] (n=1)	Case report	NA	30	NA	NA	Yes	Yes	Yes	Yes	Yes
Gupta et al[7] (n=1)	Case report	NA	35	26	Idiopathic	Yes	Yes	Yes	Yes	Yes
Panda 2014[8] (n=1)	Case report	NA	56	28.6	Idiopathic	Yes	Yes	Yes	No	Yes
Present study (n=4)	Case series	4/1175 (0.3)	26.2±6.4	24.2±4.7	Idiopathic	All	1/4 (25)	1/4 (25)	1/4 (25)	All

B. Polysomnography and multiple sleep latency test parameters of 28 narcolepsy patients

Author	Sleep duration (min)	Sleep efficiency (%)	REM sleep (%)	RDI (events/h)	Arousal index (events/h)	Sleep latency (min)	REM latency (min)
Gupta et al[4] (n=20)	421±85.8	79.4±12.4	36.7±3.5	0.4±1.1	18.7±10.3	1.3±0.3	2.5±0.6
Bhatia and Arif[5] (n=1)	NA	NA	NA	Normal	NA	0.46	Short
Shehna et al[6] (n=1)	NA	NA	NA	NA	NA	0.25	5
Gupta et al[7] (n=1)	310	96	Normal	2	NA	0.7	8
Panda[8] (n=1)	NA	94.9	27.9	Normal	NA	1.4	Short
Present study (n=4)	461.7±47.5	92±4.9	17.8±5.2	0.8±1.05	38.5 (14.5-61.9)*	2.7±1.3	5.7±2.9

Data expressed as mean±SD; *Data expressed in median (interquartile range). EDS, excessive daytime sleepiness; REM, rapid eye movement; RDI, respiratory distress index; NA, not available; SD, standard deviation; BMI, body mass index

reported Indian data[4]. However, data from other countries suggest that the occurrence of narcolepsy is maximum in the second and fourth decades[3,14]. This contrasting feature could be due to late presentation or appreciation of symptoms of 'excessive sleepiness' in the second decade, which is often thought to be innocuous or dismissed as a sign of laziness or tiredness. Male gender dominance in global as well as Indian data suggested that males were at higher risk of suffering from narcolepsy (1.6-1.8 males per 1 female)[3]. This gender difference could be attributed to referral bias or underuse of medical facilities by female patients or unknown role of gender in the narcolepsy. A study from India by Sureshbabu *et al*[15] (not included in the review table), also showed the onset of narcolepsy in the third decade, and males were shown to be more affected by narcolepsy. In our study, the mean sleep latency and REM sleep percentages were different from the previous Indian studies[4,8] but similar to previously reported studies from other countries[16,17].

Merit of the current study was a review of PSG and MSLT records with exclusion of other coexisting sleep disorders. Limitations of the study included retrospective nature of the study; hence, some information about patients might have been missed and MSLT was not done in all patients with EDS. Furthermore, HLA genotyping and CSF hypocretin level estimation were not done.

In conclusion, the present results suggest that narcolepsy occurs rarely in India and the disease predominantly affects males in their third decade of age. In future, large population-based studies need to be undertaken to confirm genuine rarity of this sleep disorder in the Indian population.

Conflicts of Interest: None.

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