

Narcolepsy in Saudi Arabia

Demographic and clinical perspective of an under-recognized disorder

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ABSTRACT

Objectives: To assess the clinical and polysomnographic features of narcolepsy in Saudis.

Methods: All patients diagnosed to have narcolepsy in the Sleep Disorders Center at King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia between March 1998 and December 2005 based on the International Classifications of Sleep Disorders Diagnostic and Coding Manual criteria were included. A data entry form collecting the demographic, clinical features, medications, referring specialty, prior diagnoses and daytime sleepiness was used. All patients underwent polysomnography followed by multiple sleep latency.

Results: Forty-seven patients with a mean age of 28.9 ± 1.9 years were included. The mean age at onset of symptoms was 20.5 ± 1.4 years. The interval between symptoms

onset and diagnosis was 8.4 ± 1.2 years. While 22 (46.8%) of the patients were referred to the sleep disorders clinic by different specialties, 25 (53.2%) patients sought an appointment in the sleep disorders clinic directly. Only 3 patients were referred with the correct diagnosis. Nocturnal sleep quality was worse in narcoleptics with cataplexy compared to those without cataplexy.

Conclusions: Saudi patients with narcolepsy have the same clinical presentation as reported in the Western literature. Narcoleptics with cataplexy had disturbed quality compared to narcoleptics without cataplexy. A long time was reported between symptoms onset and diagnosis, which may reflect the under-recognition of the problem among physicians.

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Narcolepsy is a chronic sleep disorder producing severe sleepiness. The term narcolepsy was first coined by Gelineau¹ in 1880 to designate an illness characterized by irresistible episodes of sleep of short duration at close intervals. The first prevalence study of narcolepsy was performed 6 decades after the syndrome was described. In 1945, Soloman² studied the United States naval recruits and

found 19 narcoleptics (2 with cataplexy) in 10,000 African Americans, or a prevalence of 190/100,000. Among 100,000 Caucasians surveyed, he found only 3 narcoleptics. Two extensive prevalence studies carried out by Dement's group in Stanford^{2,4} revealed a prevalence of 50 and 60/100,000, respectively. The highest prevalence was reported from Japan, where Honda⁵ reported a prevalence of 160/100,000 in school

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children aged 12-16 years. The lowest frequency was found among Israeli Jews (0.23/100,000).⁶ In Saudi Arabia, Al Rajeh et al⁷ in a community survey of neurological disorders in Al-Thughbah (23,227 Saudis) reported a prevalence of 0.04% (40/100,000) using a pre-tested questionnaire without laboratory confirmation. Some of the variability in the incidence between different studies is related to the diagnostic criteria used. Including patients without cataplexy would increase the prevalence by approximately one third.⁸ Other possible explanations could be related to race and genetics.

Narcolepsy is characterized by irresistible attacks of sleep under unusual circumstances (example, while eating, driving the car or talking), hypnagogic (vivid) hallucinations on falling asleep or on waking (hypnopompic hallucinations), cataplexy (a sudden usually bilateral loss of muscle tone that is provoked by emotional stimuli and which can make the person fall), sleep paralysis (unpleasant generalized paralysis just before, or while falling asleep or, on waking) and disturbed nocturnal sleep.^{9,10} Great advances have been made in the understanding of this still mysterious disorder; reduced levels in the nervous system of the recently described neuropeptide hypocretin,¹¹ progress in the elucidation of the genetic control of hypocretin production and the possible role of ethnicity,¹² and, the association of this disorder with the human leukocytes antigen system, which had suggested that autoimmunity may play a role.¹³ In most cases, symptoms begin during teenage or young adult years. However, the disorder may first be evident in the very young or in middle-aged adults.¹⁴ We conducted this study to answer the following questions: 1. What are the clinical features of Saudi patients with narcolepsy, the time interval between symptoms onset and the correct diagnosis, diagnoses received prior to narcolepsy diagnosis, the referring specialties (including self-referral), the chronological order of appearance of symptoms and any associated precipitating factors? 2. What are the polysomnographic (PSG) and multiple sleep latency (MSLT) characteristics of patients with narcolepsy and the prevalence of other co-existing primary sleep disorders? 3. What are the pharmacotherapeutic modalities used, the patient's response, and documented side effects? and finally, 4. to compare our results to published data.

Methods. The study was conducted in the Sleep Disorders Center (SDC) at King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia. King Khalid University Hospital accepts referrals from all

over the country, and referrals are sent to the SDC from all provinces in the country.

All patients referred to the SDC with the complaint of excessive daytime sleepiness (EDS) are evaluated clinically before undergoing PSG. Following PSG, patients with the clinical suspicion of narcolepsy undergo multiple sleep latency testing (MSLT). For the clinical diagnosis of narcolepsy, we used the guidelines of the International Classifications of Sleep Disorders Diagnostic and Coding Manual.¹⁵ Patients who met the minimal criteria for the diagnosis of narcolepsy from March 1998 until December 2005 were included. There are 2 sets of minimal criteria for the diagnosis of narcolepsy: The first includes the combination of recurrent daytime naps or sleep attacks that occur almost daily for at least 3 months and the presence of sudden muscle weakness (cataplexy). The second is the combination of sleepiness or sudden muscle weakness (cataplexy) plus associated features, which may include sleep paralysis, hypnagogic hallucinations, automatic behaviors, disruptive major sleep episodes and PSG findings demonstrating one or more of: sleep latency <10 minutes; rapid eye movement (REM) latency <20 minutes, an MSLT demonstrating a mean sleep latency of <5 minutes; 2 or more sleep onset REM periods; and the absence of any documented medical or psychiatric disorders that could account for the symptoms. All of our patients met one of the sets of diagnostic criteria.

Patients with medical conditions causing sleepiness like hypothyroidism, a medication such as benzodiazepines or sleep deprived patients based on sleep diary (sleeping less than 7 hours per 24 hours) were excluded. All patients were evaluated by a psychiatrist to rule out psychiatric disorders.

A data entry form collecting the demographic, clinical features, medications, referring specialty, prior diagnoses and daytime sleepiness was used. Subjective sleepiness was assessed using the Epworth Sleepiness Scale (ESS). The Epworth Sleepiness Scale is a specialized, validated sleep questionnaire containing 8 items that ask for self-reported disclosure of the expectation of dozing in a variety of situations.¹⁶

Alice-4 and Alice-5 diagnostic equipment from Respirationics, USA were used in data acquisition. During PSG, the following parameters were monitored: brain activity by 4 electroencephalographic placements (C1-A4, C2-A3, O1-A4, and O2-A3); muscle tone by chin and leg electromyography (EMG); eye movements by electro-oculography; heart rate by electrocardiography; oxygen saturation by finger pulse oximeter; chest and abdominal wall

movements by thoracic and abdominal belts; air flow by thermistor and nasal prong pressure; sleep position by position sensor; and snoring by microphone.

All sleep studies were analyzed by one of the authors to maximize the inter-scorer and intra-scorer reliability. Studies were analyzed for light off, light on, time in bed, total sleep time (TST), sleep period time, and sleep latency. Scoring included the sleep stages and percentages of TST, REM latency, and duration, number of REM cycles and arousals according to established criteria.^{17,18} Periodic leg movements were scored using Coleman's criteria.¹⁹ Obstructive sleep apnea was defined as apnea hypopnea index >5/hour. Reports were generated using the Alice-4 and 5 software.

Standard MSLTs were performed in accordance with the American Academy of Sleep Medicine guidelines²⁰ following PSG. Manual analysis of the MSLT data included sleep latency from lights out to first epoch of sleep, mean latencies to sleep for all naps and number of sleep-onset REM (SOREM) periods. Four to 5 tests (naps) 2 hours apart were performed beginning 1.5 to 2 hours after awakening in the morning. Routine hook up was carried out after omitting leg EMG and cardio-respiratory parameters. Sleep was defined as 3 consecutive epochs of stage one sleep, or after one epoch of any other stage of sleep. The test was continued for 15 minutes after sleep onset to document the presence or absence of REM sleep. Sleep latency was averaged over all naps and indicated on the report form.

Statistical analysis. Data were expressed as mean \pm standard error of the mean. Comparisons of numerical variables were analyzed by Student's t-test; if the normality test failed, the rank sum test was used. Categorical variables were compared using chi-square or Fisher's exact tests. All statistical analyses were performed using Sigma Stat, Version 3 (SPSS Inc, Chicago, Illinois, USA) statistical software. A *p* value <0.05 defined statistical significance.

Results. A total of 47 patients were diagnosed with narcolepsy during the study period with a mean age of 28.9 ± 1.8 years (range 9-65 years). Males constitute 72% of patients. The mean age at onset of symptoms was 20.5 ± 1.4 years. The time between symptoms onset and diagnosis was 8.4 ± 1.2 years. The mean ESS was 17.5 ± 0.7 , and the mean body mass index was 29.6 ± 0.9 kg/m². While 22 (46.8%) of the patients were referred to the sleep disorders clinic by different specialties, 25 (53.2%) patients sought an appointment in the sleep disorders clinic directly. Among the patients who were referred to the SDC, only 3 patients were referred with the correct diagnosis of

narcolepsy. The remaining patients received different diagnoses; one as insomnia with daytime sleepiness, one as obstructive sleep apnea, 2 as normal who were referred upon their requests and the rest as EDS for investigation. **Table 1** presents the demographic and clinical characteristics of the whole group. All patients reported that symptoms appeared simultaneously. No chronological order could be recalled. Thirty-four (72%) patients had cataplexy. Cataplexy manifested as complete muscle weakness and collapse in 7 (22%) and partial weakness in the rest. Partial attacks were knee weakness, jaw sagging, inclination of the head and weakness of the hands. Laughter was the most common provoking emotion (60%) followed by anger (40%) and other emotions like sadness and amusement (16%). Narcoleptics were then divided into those with cataplexy and those without. **Table 2** demonstrates the clinical characteristics of both groups. The time difference between symptoms onset and diagnosis was significantly longer in the cataplexy group. However, the cataplexy group was younger at the onset of symptoms, although the difference did not reach statistical significance. Sleep paralysis and the complaint of nocturnal sleep interruption were more common in the cataplexy group. **Table 3** demonstrates the PSG and MSLT characteristics of both groups. Sleep onset and REM latency were significantly shorter in the cataplexy group. The percentage of stage one per TST was significantly longer in the cataplexy group. The MSLT REM latency was significantly shorter in the cataplexy group, and the number of SOREM episodes was significantly more in the cataplexy group. No difference in MSLT sleep latency was demonstrated between the 2 groups.

In addition to behavioral therapy, 36 patients were treated with modafinil. The average daily dose needed to control sleepiness was 259.4 ± 14.8 mg. Six patients were on methylphenidate (MP). Four of them needed 400 mg of modafinil and MP to control their symptoms. The average daily dose of MP was 28 ± 13.6 mg. One patient continued to have significant daytime sleepiness despite getting modafinil 400 mg and MP 80 mg daily. Two patients on MP, and one patient on modafinil developed severe gingivitis while on treatment. Gingivitis disappeared upon stopping the treatment. All 3 patients had poor dental hygiene to start with. One patient developed severe headache while on modafinil that necessitated stopping the drug and shifting him to MP. Blood pressure was monitored frequently while all patients were on treatment. No elevation in blood pressure was documented. To control the cataplectic attacks in patients with cataplexy, fluoxetine was used in all patients. The average dose was 23.7 ± 2.6 mg

Table 1 - Clinical features of patients with narcolepsy

Clinical and demographic data	Number (%)
Irresistible attacks of sleep	47 (100)
Cataplexy	34 (72)
Sleep paralysis	27 (57.4)
Interrupted sleep	18 (38.3)
Hypnagogic hallucinations	40 (85.1)
OSA (AHI>5/hr)	12 (25.5)
PLM index >5/hr	31 (66)
On modafinil	36 (76.6)
On Methylphenidate (MP)	6 (12.8)
On modafinil and MP	4 (8.5)

OSA - obstructive sleep apnea, PLM - periodic legs movements, AHI - apnea hypopnea index

Table 2 - Demographic and clinical characteristics of patients with and without narcolepsy

Characteristics	Patients with cataplexy N=34	Patients without cataplexy N=13	P-value
Age at onset	20.5 ± 1.4	25.5 ± 3.1	NS
Age at diagnosis	28.9 ± 1.8	25.5 ± 3.1	NS
Gap between symptoms onset and diagnosis (years)	8.4 ± 1.2	3.4 ± 0.8	0.02
Epworth sleepiness scale	18.4 ± 0.6	16.2 ± 2.0	NS
Interrupted sleep	18 (51)	1 (8)	0.056
Sleep paralysis	26 (74)	2 (17)	0.007
Hypnagogic hallucination	34 (97)	7 (60)	NS

Table 3 - Polysomnographic and multiple sleep latency characteristics of patients with and without narcolepsy

Characteristics	Patients with cataplexy N=34	Patients without cataplexy N=13	P-value
Apnea hypopnea index	8.8 ± 2.8	8.0 ± 3.4	NS
Wake after sleep	46.9 ± 5.9	37.7 ± 14.6	NS
Sleep onset (min)	5.6 ± 1.1	10.0 ± 2.6	0.04
Latency to rapid eye movement (min)	56.9 ± 14.2	98.2 ± 18.9	0.02
Stage shifts	87.0 ± 6.8	65.0 ± 10.9	NS
Sleep efficiency	83.4 ± 2.5	85.5 ± 4.7	NS
Stage 1%	14.9 ± 2.3	6.03 ± 1.7	0.02
Stage 2%	50.7 ± 3.4	65.9 ± 2.7	0.008
Deep sleep %	11.0 ± 1.4	11.5 ± 1.8	NS
Rapid eye movement (%)	20.8 ± 2.8	15.4 ± 2.5	NS
Rapid eye movement cycles	3.2 ± 0.2	3.2 ± 0.6	NS
Arousals rapid eye movement	22.4 ± 4.2	12.3 ± 4.6	NS
Arousals non-rapid eye movement sleep	90.8 ± 22.0	68.9 ± 18.6	NS
Arousal index	27.0 ± 4.1	17.0 ± 3.5	NS
Sleep latency (MSLT)	2.2 ± 0.4	2.8 ± 0.7	NS
Rapid eye movement latency (MSLT)	2.8 ± 0.4	4.3 ± 0.8	0.09
Sleep onset rapid eye movement (MSLT)	3.4 ± 0.12	2.2 ± 0.3	0.002

MSLT - multiple sleep latency

daily. Three patients continued to have cataplexy despite taking 80 mg of fluoxetine. In that group of patients, the dose of fluoxetine was gradually reduced and imipramine or clomipramine was added, which resulted in a significant improvement in symptoms. Fluoxetine had to be stopped in one patient, and imipramine in another patient due to impotence. No other serious side effects that necessitated stopping the drug were reported.

Discussion. Narcolepsy is a rare disorder, which is under-recognized by many physicians.²¹ The clinical picture of narcolepsy consists of a tetrad of symptoms; irresistible attacks of sleep, cataplexy, hypnagogic hallucination, and sleep paralysis. Some patients may also complain of disturbed nocturnal sleep. Previous reports demonstrated that 10-15% of patients experience the full tetrad.²² In our patients, 27.7% experienced the full tetrad. Symptoms usually develop gradually. It may take several years for each subsequent symptom to occur.²³ However, our patients could not recall any chronological difference in the order of appearance of symptoms. The clinical features of our patients were consistent with the reported literature. Our results concur with previously published reports, which demonstrated that narcolepsy is more prevalent in males.⁸ In our study, 27.7% of our patients were diagnosed to have narcolepsy without cataplexy, as compared to 25-35% in the West.^{8,24} It has been suggested that narcoleptics with cataplexy have disturbed quality of sleep compared to narcoleptics without cataplexy.²⁵ In a retrospective analysis of 157 patients with narcolepsy, Aldrich²⁶ reported that narcoleptics with cataplexy had less deep sleep, greater awakenings, and more stage one sleep compared to narcoleptics without cataplexy. Additionally, the group with cataplexy had a higher incidence of sleep paralysis and sleep-related hallucinations. Similar findings were reported in our patients. Since stage one sleep occurs throughout the night as a transitional stage,²⁷ a significant increase in stage one sleep may be regarded as an indicator of sleep disruption.

The interval between symptoms onset and diagnosis was more than 8 years. It has been demonstrated that the interval between symptoms onset and diagnosis may exceed a decade.²⁸ Most of our patients did not receive a specific diagnosis by the referring physicians. Instead, they were labeled with a chronic symptom without diagnosis. It has been demonstrated that narcoleptics are more likely than controls to receive a wide variety of mental and neurological diagnoses prior to the correct diagnosis.²¹ The above may partially explain the

delayed diagnosis in narcolepsy patients. The delayed diagnosis cannot be explained on the basis of lack or reduced access to the health care services as it has been shown that narcolepsy patients had twice as many contacts with doctors and saw more doctors.²¹ The latter finding supports the hypothesis that in many patients with narcolepsy, the diagnosis was missed by the treating clinicians. Based on our experience, such patients are labeled as lazy with mental disorders. Moreover, cataplexy can be very embarrassing to the afflicted patients, especially the very young patient. Sleep disorders in general, and narcolepsy in particular, are under-recognized and probably under-diagnosed. Many physicians lack the basic education in sleep medicine. A survey conducted in the United Kingdom (UK) in 1998 revealed that undergraduate courses devoted a median of 5 minutes to sleep and its disorders.²⁹ Another survey conducted among primary care physicians in the Riyadh area in 1999, demonstrated great deficiencies in the theoretical and clinical knowledge of the studied physicians in sleep medicine and sleep disorders.³⁰

Treatment of narcolepsy can be divided into behavioral therapy and pharmacotherapy. Pharmacotherapy in the treatment of narcolepsy has significantly changed over the past few years. Methylphenidate was introduced initially by Daly and Yoss³¹ in 1956 to treat sleepiness in narcoleptics. At present, modafinil is the drug of choice for sleepiness in narcolepsy. It has been approved for the treatment of narcolepsy in France since 1992, in United States (US) and UK since 1998, Italy since 2000 and Australia and New Zealand since 2002. We started using modafinil in Saudi Arabia in 2002. The modafinil daily dose ranges from 100-400 mg. As modafinil is relatively expensive (one tablet of 200 mg costs SR35-37), we reviewed our experience with this drug in Saudi patients. In general, the drug was well tolerated. Two patients had to stop treatment; one due to severe headache and one due to severe gingivitis. Headache has been reported in 13% in the US modafinil multicenter study.²⁸ To our knowledge, gingivitis has not been reported before as a side effect of modafinil or MP. In 4 patients, modafinil efficacy was insufficient. Hence, modafinil was supplemented with MP on as needed basis or at times when sleepiness is most severe. It is worth mentioning here that one of the limitations of modafinil is its liver metabolism, and its ability to induce certain liver enzymes, which lead to numerous drug interactions that should always be taken into consideration if other drugs are co-administered.³²

In summary, the study demonstrated that Saudi patients with narcolepsy have the same clinical profile

as reported in the Western literature. Narcoleptics with cataplexy had disturbed sleep quality compared to narcoleptics without cataplexy. A long interval was reported between symptoms onset and diagnosis, which may reflect under-recognition of the problem among physicians. Modafinil was well tolerated among patients.

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