Clinical Aspects of Narcolepsy-Cataplexy Across Ethnic Groups

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Study Objectives: The objectives of this study were to compare severity and clinical presentation for narcolepsy-cataplexy across various ethnic groups. A large sample of narcoleptic patients was also used to further describe symptomatology and natural history for this sleep disorder.

Design: Retrospective review of clinical data ascertained from the Stanford Sleep Inventory, polysomnography and MSLT data, as well as clinical notes. Ethnicity was narrowly defined as African (Black) Americans, Caucasians, Asians, and Latinos when both parents and the subject identified with a given ethnic group.

Setting: N/A

Participants: We compared the severity and clinical presentation of narcolepsy in 64 African Americans, 353 Caucasians, 32 Asians, 26 Latinos, and 9 subjects of mixed ethnicity. Subjects were recruited through the Stanford center for narcolepsy research.

Interventions: N/A

Measurements and Results: A striking similarity in symptomatology, age of onset, and disease severity was found across ethnic groups. Mean age of onset for sleepiness, hypnagogic hallucinations, sleep paralysis and cataplexy were 19.20, 19.50, 20.11 and 23.02 years old. We also found that narcoleptic patients have slightly but significantly elevated body mass index relative to normative data (106.6% of matched controls, $p<0.005$) and are born slightly more frequently during the month of March. A tight correlation between our previously validated cataplexy scale and DQB1*0602 positivity was observed. Two thirds of patients reported having cataplexy with laughing, 92% of those being DQB1*0602 positive independent of ethnicity.

Conclusions: These results confirm the similarities in clinical presentation and natural history of narcolepsy-cataplexy in a large number of patients of various ethnic groups and cultural backgrounds.

Key words: Narcolepsy; cataplexy; HLA; ethnicity; season of birth

INTRODUCTION

NARCOLEPSY IS A LIFE-LONG NEUROLOGICAL DISORDER CHARACTERIZED BY EXCESSIVE DAYTIME SLEEPINESS AND ABNORMAL REM SLEEP EVENTS SUCH AS CATAPLEXY (the sudden loss of muscle tone triggered by an emotional stimulus, i.e., laughing, anger, or joking), hypnagogic hallucinations (dream-like experiences occurring at sleep onset), and sleep paralysis (the inability to move while falling asleep or upon awakening).[1,2] Individuals with narcolepsy have shortened latency to sleep onset, and typically exhibit two sleep-onset REM periods during the Multiple Sleep Latency Test (MSLT).[3] In addition to these primary objective symptoms, patients often experience disturbed nocturnal sleep, automatic behavior and short-term memory problems. A large number of investigators have identified cataplexy as the most specific symptom of the narcolepsy syndrome.[1,2,4-6] Recent studies have shown that most cases of narcolepsy-cataplexy are associated with a deficiency in hypocretin (orexin) neurotransmission in the brain, possibly as the result of an autoimmune mediated process.[7-10]

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Narcolepsy-cataplexy is not an uncommon condition. Population-based studies indicate a consistent prevalence rate of 1/2,000 in North American and Western European countries.[11,12] Outlier prevalence rates include a low 0.002% in Israel[13] and a high 0.16% value in Japan,[14] but these studies have used less stringent designs and need confirmation.[12] Only one study, a 1945 study in Army recruits, has measured prevalence in African Americans.[15] The observed figure was 0.02% (2/10,000) for narcolepsy-cataplexy and 0.19% for narcolepsy without cataplexy. This figure was contrasted with an unusually low prevalence of 0.004% (4/100,000) in Caucasians. Interpretations for this last study included a "constitutional predisposition toward the development of narcolepsy" and statements such as "the educational, cultural and social position of the [African American], particularly in the south in this country, may make sleep seem more attractive than nature had intended,"[15] Despite these few exceptional cases, our current interpretation of the data is that there is little in the literature genuinely supporting differences in prevalence and symptomatology across ethnic groups. Similarly, some studies have suggested increased prevalence of sleep paralysis in African American and Asian controls, an observation that needs replication.[16-18]

The observation that narcolepsy is tightly associated with HLA positivity across various cultural and ethnic groups[19-21] indirectly demonstrates the etiological homogeneity of the syndrome. In the late 1980s, the finding that African American patients were more frequently HLA-DR2 negative than Caucasian and Japanese patients raised the possibility of inter-ethnic differences.[22] This discrepancy was soon resolved with the finding that HLA-DQB1*0602 rather than DR2 is the unifying susceptibility allele across ethnic groups.[20,21] However, approximately 12% of Japanese, 25% of Caucasian, and 38% of African

Table 1—Demographic characteristics of the sample across ethnic groups

Ethnic group	Caucasian	Black	Asian	Latino	Mixed	p-value†
Number of subjects	353	64	32	26	9	
Sex (% Male)	42.8 (151)	40.6 (26)	59.4 (19)	46.2 (12)	22.2 (2)	
Age (years)	43.6±0.9 (350)	46.2±1.8 (63)	38.6±3.1(32)	38.6±2.4 (25)	31.4±2.7 (8)	p <0.05
% 0602 positive	81.3 (278/342)	88.7 (55/62)	96.7 (29/30)	85.7 (12/14)	66.9 (6/9)	
Body Mass Index (BMI, kg/m2)	27.5±0.3 (331)	30.5±1.0 (59)	25.1±0.8 (23)	26.9±1.4 (25)	23.3±1.3 (8)	
cBMI[a] (kg/m^2)	26.8±0.1 (302)	28.4±0.3 (58)	23.2±0.8 (6)	26.2±0.2 (25)	25.6±0.4 (8)	
pBMI[a] (kg/m^2)	27.5±0.3 (329)	30.6±1.0 (59)	25.1±0.8 (21)	26.9±1.4 (25)	23.3±1.3 (8)	p = 0.001
% BMI[b]	106.7±3.7 (302)	108.5±3.3 (58)	118.8±7.8 (6)	103.0±5.6 (25)	91.1±5.5 (8)	p <0.001

Data are mean ±SEM or %. [a]cBMI are expected control BMI values tabulated for each narcoleptic subject using normative data based on each narcoleptic's respective country of origin, age and gender. The normative data was obtained from the United States, the Czech Republic, Holland, and Japan. [b]%BMI is the ratio of BMI over cBMI for every subject. pBMI are patient values with associated cBMI. †: Effect of ethnicity estimated using general linear regression analyis performed controlling for age and gender. *= p=0.05 versus cMBI using a paired t-test.

American controls are DQB1*0602 positive.[21]

Another source of confusion in defining an etiologically homogeneous disease entity for narcolepsy is the nosological definition of the syndrome and its components. Clinical studies and HLA typing studies have long led to the conclusion that cataplexy is the most specific symptom of the syndrome, with probable disease heterogeneity in patients without cataplexy.[23] HLA-DQB1*0602 positivity is especially high (e.g., 90%-100%) in patients with definite cataplexy, but decreases dramatically with atypical or no cataplexy (40%).[6] Even in cataplectic patients, substantial differences in HLA association have been reported (70%-100%).[6] This has prompted some researchers to believe that cataplexy may be overdiagnosed in some cases. One possible explanation for this problem may be the imprecise definition of cataplexy currently listed in international classifications. In a recent study, a questionnaire focusing on cataplexy was administered to 983 successive sleep disorders patients, 63 of which had narcolepsy-cataplexy.[5] The goal of this study was to standardize the evaluation of cataplexy. A critical finding was the report that 30% of the non-narcoleptic population reports "muscle weakness episodes triggered by emotions" using the current ICSD 10 definition for cataplexy.[24] We also identified that cataplexy was best defined when triggered by a particular pattern of emotions. Specifically, joking and anger were the most precise combination of triggers for cataplexy. Approximately half of the narcolepsy population reported such a pattern of triggers vs. 0.3% of non-narcoleptics. Other specific triggers were joking without anger and laughing independent of joking.[5]

In this study, a large sample of 484 randomly recruited narcoleptic patients was used to contrast the clinical picture across ethnic groups and to further describe the natural history and symptomatology of narcolepsy. To avoid possible issues with disease heterogeneity, we focused our attention on cases reporting cataplexy during clinical interview and confirmed by the Stanford Sleep Inventory.

METHODS

Patients

Patients were identified by clinicians in the United States (n=395), Canada, Europe (Czech Republic, England, France, Norway, Turkey) and Asia (China, Japan, Korea, Malaysia) over a 15-year period. Four hundred and eighty-four unrelated subjects with a diagnosis of narcolepsy-cataplexy based on international classification of sleep disorders criteria were studied. These subjects were recruited independently of family history, sex, or HLA status and represent a random sample. All patients gave informed consent for the study. The only other criterion for inclusion was the completion of our previously validated Stanford Sleep Inventory (SSI, see: http://www-med.stanford.edu/school/Psychiatry/narcolepsy/)[5] and donation of a blood sample for HLA typing. Ethnicity was narrowly defined as African (Black) Americans, Caucasians, Asians, and Latinos when both parents and the subject identified with a given ethnic group. Other subjects were considered of "mixed" ethnic group (see SSI questions on ethnicity for details). Mean age (±SEM) was 43.1±0.7 years, with 43.4% male. Subjects included 353 Caucasians, 64 African Americans, 32 Asians, 26 Latinos, and 9 subjects of mixed ethnic groups. Various demographic variables for the samples are reported in Table 1.

Evaluation of symptomatology

Most of the data was collected using the SSI. Additional information regarding nocturnal polysomnography and MSLT data was collected on a case by case basis by gathering copies of medical reports. Daytime sleepiness was assessed by the Epworth Sleepiness Scale score and questionnaire items, such as reported number of naps taken in a week and MSLT data. The presence, description, and severity of cataplexy, hypnagogic hallucinations, sleep paralysis, and disturbed nocturnal sleep were assessed

Table 2—Demographics by HLA type

	0602+	0602-	p-value
Number of subjects	380	78	
Sex (% Male)	43.1	47.4	
Age (years)	44±0.9(378)	38.8±1.4(78)	p<0.01
Body Mass Index (BMI)[a]	28±0.3(352)	26.1±0 .7(72)	
% Caucasian	73.2	82.1	

[a]Non significant, general linear regression performed controlling for age and gender

using questionnaire data. Additional data collected included self-reported ages of onset for all symptoms, specific cataplexy triggers and their frequencies, muscle groups affected, and usual duration of attacks.

HLA Typing

The presence or absence of HLA-DQB1*0602 was evaluated using a combination of techniques developed over several years. Most samples were HLA DQ typed using Innotype reverse dot blot kits[6] according to the manufacturer's recommendations (Robbins Scientific, Sunnyvale, CA USA). Other samples were DQB1*0602 typed using sequence-specific primers 611F and 611R.[25] A few remaining samples were typed using PCR oligotyping techniques.

Data Analysis

Clinical symptoms, Epworth Sleepiness Scale, and MSLT data were stratified by ethnicity and HLA-DQB1*0602 status. The decision tree proposed by Anic-Labat et al.[5] was used to categorize cataplexy (category 1: episodes not triggered by either laughing or joking; category 2: episodes triggered by joking but not anger or episodes triggered by laughing alone; category 3: episodes triggered by joking and anger). All comparisons were performed using linear regression, chi-squares, and/or logistical regression with control of potentially confounding variables when appropriate. Data was analyzed using SYSTAT version 10.0.

Month of birth analysis was performed utilizing χ^2 using the U.S. narcolepsy sample in comparison with a matched sample drawn from the National Center of Health Statistics. To do so, each subject of a given year and month was assigned control values for each month corresponding to the number of births reported that month of that year divided by the total number of births that year. All of these controls were then added to create an artificially matched sample of monthly births of similar sample size. For Body Mass Index (BMI) analysis, normative data was obtained by age, sex, and ethnicity for the United States, the Czech Republic, Korea, and Japan. A control BMI (cBMI) value was tabulated for each narcoleptic subject using normative data. Statistical differences between narcolepsy (pBMI) and controls (cBMI) were evaluated using paired t-test across the entire ethnic set and by ethnic groups. Inter-ethnic differences were evaluated using linear regression, controlling for confounding variables.

RESULTS

Increased Body Mass Index (BMI) in Narcoleptic Patients

When compared to control BMI matched by ethnicity, age, sex, and country of origin, narcoleptic patients were found to have marginally but significantly higher BMI. In 399 patients with available matched control values, mean pBMI was 27.92 compared to a mean matched value of 26.91 (paired t test=-3.22, mean difference=-1.00±0.31, p=0.0014). BMI also differed across ethnic groups (F = 4.35, p = 0.002), with higher values being observed in Asians and African Americans. This difference was also reflected when BMI was normalized as a percent of control values. Overall %BMI value was 106.6% of matched control values, with significant variation across ethnic groups (Table 1). In contrast with this effect, BMI did not differ by HLA-DQB1*0602 status (Table 2). A higher BMI was observed in HLA positive subjects but the difference was due to the significantly older age of these subjects (Table 2).

Clinical Symptomatology Across Ethnic Groups

Very few differences in the severity and presentation of symptoms were observed between ethnic groups. Asian subjects generally reported less cataplexy in association with negative emotions such as anger, a probable cultural difference. Other minor differences included the higher report of cataplexy affecting the jaw and arms in Caucasian patients and differences in answering the question "do you ever go blank (because of sleep attack)" during various situations (Table 3). We also found that occurrence of sleep paralysis did not differ across ethnic groups, but was less severe in Caucasians (Table 3).

Clinical Symptomatology and HLA Status

Many differences were found between the two HLA typed groups, with generally more severe and typical symptoms in HLA positive subjects. As previously reported, cataplexy was more often triggered by positive emotions and affected more typical muscle groups such as legs, knees, jaw and head (Table 4).[6] Usual duration of cataplexy was shorter in HLA positive subjects, but the frequency of events was higher in HLA positive subjects. Age of onset for cataplexy, sleep paralysis, hypnagogic hallucinations and sleepiness were all higher in HLA positive subjects. HLA typing was also examined in relation to specific cataplexy triggers as defined in Anic-Labat et al.[5] (Figure 1). A surprising correlation of HLA typing was found with the most specific trigger for cataplexy, joking. Ninety-two to 93% of patients answering yes to cataplexy (2/3 of 482 subjects) when joking were HLA positive. This correlation was independent of ethnicity (data not shown).

We also extended the study to look at other clinical features and found more severe daytime sleepiness in HLA positive subjects as measured using the MSLT and the Epworth Sleepiness Scale. Disturbed nocturnal sleep was also more severe in HLA positive subjects. Interestingly, severity scores for hypnagogic hallucinations and sleep paralysis were higher in HLA negative subjects, but similar rates of occurrence were seen in spite of less

Table 3—Clinical and polysomnographic variables across ethnic group

Ethnic groups		Caucasian (n=351)	Black (n=64)	Asian (n=32)	Latino (n=26)	Mixed (n=9)	p-value
Cataplexy							
Triggers[a]	Positive Emotions	95.7 (336/351)	93.8 (60/64)	96.9(31/32)	96.2 (25/26)	100 (9/9)	
	Negative Emotions	77.8 (273/351	89.1 (57/64)	62.5 (20/32)	88.5 (23/26)	77.8 (7/9)	p<0.05
	Not Defined Emotions	82.6 (290/351)	89.1 (57/64)	81.3 (26/32)	92.3 (24/26)	66.7 (6/9)	
	Weakness in legs/knees	98.3 (345/351)	93.8 (60/64)	100 (32/32)	100 (26/26)	100 (9/9)	
	Jaw dropping/sagging	75.6 (263/348)	50.8 (32/63)	53.1 (17/32)	60.0 (15/25)	33.3 (3/9)	p<0.001
Localization	Head/shoulders dropping	75.6 (263/348)	76.2 (48/63)	71.9 (23/32)	68.0 (17/25)	44.4 (4/9)	
	Weakness in arms	83.0 (289/348)	71.4 (45/63)	62.5 (20/32)	76.0 (17/25)	88.9 (8/9)	p<0.05
	Slurred speech	71.8 (250/348)	65. (41/63)	65.6 (21/32)	64.0 (16/25)	66.7 (6/9)	
	Injured from weakness	33.1 (111/335)	40.0 (22/55)	33.3 (10/30)	24.0 (6/25)	25.0 (2/8)	
	5-30 seconds	61.8 (210/340)	60.3 (35/58)	70.0 (21/30)	56.0 (14/25)	55.6 (5/9)	
Usual Duration	30 seconds - 2 minutes	25.3 (86/340)	22.4 (13/58)	13.3 (4/30)	16.0 (4/25)	33.3 (3/9)	
	> 2 minutes	12.9 (44/340)	17.2 (10/58)	16.7 (5/30)	28.0 (7/25)	11.1 (1/9)	
	>1/day - several/week	57.9 (191/330)	54.7 (29/53)	46.7 (14/30)	52.0 (13/25)	55.6 (5/9)	
Frequency	1/week	22.7 (75/330)	28.3 (15/53)	26.7 (8/30)	28.0 (7/25)	11.1 (1/9)	
	1/month	12.4 (41/330)	11.3 (6/53)	23.3 (7/30)	16.0 (4/25)	33.3 (3/9)	
	1/year or less	7.0 (23/330)	5.7 (3/53)	3.3 (1/30)	4.0 (1/25)	0 (0/9)	
Age of Onset (years)		22.7±.6	25.1±1.8	25.1±2.4	21.0±1.7	19.3±2.5	
Daytime Sleepiness and Nocturnal Sleep							
Epworth Sleepiness Scale (score)		18.0±.2 (347)	18.5±.6 (61)	17.3±.8 (32)	19±.7 (26)	16.8±1.0 (9)	
Napping (#/Week)		8.2±.4 (219)	8.3±1.3 (30)	10.4±1.5 (32)	8.5±1.3 (20)	5.5±1.5 (8)	
Age of Onset (years)		18.5±.6 (217)	17.7±1.8 (29)	17.8±1.9 (31)	18.3±1.4 (19)	17.1±2.9	
Multiple Sleep Latency Test (sleep latency, min)		2.9±.2 (280)	2.4±.2 (52)	2.9±.5(21)	1.6±.5 (7)	3.3±1.1 (5)	
Multiple Sleep Latency Test (# SOREMPs)		2.9±.1 (280)	2.8±.2 (52)	3.1±.3 (21)	2.9±.6 (7)	1.8±.9 (5)	
Disturbed Nocturnal Sleep (# of Awakenings per Night)		4.0 ± .3 (220)	4.5±1.7 (30)	2.8±.3 (32)	3.8±1.5 (19)	4.5±2.3 (8)	
Going Blank while Driving (% Yes)		63.0 (133/211)	60. (15/25)	40.0 (12/30)	60.0 (12/20)	37.5 (3/8)	
Going blank in various situations (%Yes)		76.5 (163/213)	91.7 (22/24)	53.1 (17/32)	55.0 (11/20)	75.0 (6/8)	p<0.01
Hypnagogic Hallucinations							
Occurence (% Yes)		75.4 (263/349)	75.4 (46/61)	78.1 (25/32)	73.1(19/26)	77.8 (7/9)	
% Frightening		79.8 (130/163)	81.8 (18/22)	80.0 (20/25)	93.3 (14/15)	66.7 (4/6)	
Severity[b] (score)		5.2±.2 (162)	6.0±.4 (21)	4.8±.4 (23)	6.1±.3 (14)	5.8±.7 (6)	
Age of Onset (age)		19.6±.9 (151)	16.2±2.6 (17)	22.1±2.7 (22)	18.6±2.1 (14)	14.8±.4 (5)	
Sleep Paralysis							
Occurrence (% Yes)		72.5 (253/349)	80.3 (49/61)	62.5 (20/32)	84.6 (22/26)	88.9 ± (8/9)	
Severity[c] (score)		4.9±.3 (163)	6.5±1(24)	6.3±.9 (19)	8.1±1 (17)	5.9±1.3 (7)	p<0.01
Age of Onset (years)		20.5±.9 (134)	17.1±2.7 (14)	19.0±2.9 (18)	20.9±2.2 (18)	17.8±3.5 (5)	

Data are mean±SEM or %. [a] Triggers refer to emotions triggering cataplectic episodes. Positive emotions: laughing, telling, or hearing a joke, excitement, elation, playing an exciting game, having to make a quick verbal response in a playful or funny context, during sexual intercourse, remembering a happy moment. Negative emotions: anger, embarrassment, stress, tension, when disciplining children. Not defined emotions:surprise, being startled, when having a romantic thought or moment, during or after athletic activities, being moved by something emotional. [b] The severity score, ranging from 0-8, is determined by a series of questions evaluating when the patient experiences images (e.g., when falling asleep abruptly, when waking in the morning, when taking a nap, and when drowsy) and when they last had such an event (e.g., past 24 hours, within the past week, within the past month, or within the past year). [c] The severity score, ranging from 0-16, is determined by assessing (1) how often the patient experiences sleep paralysis when awakening from a nap or when falling asleep (daily, several times a week, once per week, once per month, once per year of less) and (2) how long ago was such past month, past year or more than a year ago).

Table 4—Clinical and polysomnographic variables per HLA DQB1*0602 type

DQB1*0602		Postitive (n=380)	Negative (n=77)	p-value
Cataplexy				
Triggers[a]	Positive Emotions	97.4 (370/380)	88.3 (68/77)	p<0.001
	Negative Emotions	77.4 (294/380)	81.8 (63/77)	
	Not Defined Emotions	82.1 (312/380)	87.0 (67/77)	
	Weakness in legs/knees	98.4 (374/380)	94.8 (73/77)	p<0.05
	Jaw dropping/sagging	72.6 (273/376)	57.9 (44/76)	p<0.01
Localization	Head/shoulders dropping	78.5 (295/376)	56.6 (43/76)	p<0.001
	Weakness in arms	80.3 (302/376)	77.6 (59/76)	
	Slurred speech	72.6 (273/376)	63.2 (48/76)	
	Injured from weakness	33.8 (120/355)	32.9 (24/73)	
	5-30 seconds	65.1 (237/364)	47.9 (35/73)	p<0.01†
Usual Duration	30 seconds - 2 minutes	23.4 (85/364)	27.4 (20/73)	
	> 2 minutes	11.5 (42/364)	24.7 (18/73)	
	>1/day - several/week	58.4 (205/351)	45.1(32/71)	p<0.05‡
Frequency	1/week	23.6 (83/351)	25.3 (18/71)	
	1/month	12.8 (45/351)	18.3 (13/71)	
	1/year or less	5.1 (18/351)	11.3 (8/71)	
Age of Onset (years)		23.8±0.6 (n=350)	20.3±1.2 (n=64)	p<0.01
Daytime Sleepiness and Nocturnal Sleep				
Epworth Sleepiness Scale (score)		18.4±0.2 (375)	16.1±0.5 (75)	p < 0.001
Age of Onset (years)		18.9±0.6 (239)	16.1±1.1 (50)	p<0.05
Multiple Sleep Latency Test (sleep latency, min)		2.3±0.1 (294)	5±0 .4 (59)	p<0.001
Multiple Sleep Latency Test (# SOREMPs)		3.0±0.1 (294)	2.4±0.2 (60)	p<0.01
Disturbed Nocturnal Sleep (# of Awakenings per Night)		4.1±.4 (242)	2.8±.5 (52)	p<0.05
Going Blank while Driving (% Yes)		58.5 (134/229)	70.0 (35/50)	
Going blank in various situations (% Yes)		71.7 (167/233)	87.8 (43/49)	p<0.05
Hypnagogic Hallucinations				
Occurrence (% Yes)		75.5 (284/376)	74.0 (57/77)	
% Frightening		82.7 (148/179)	68.3 (28/41)	p<0.05
Severity[b] (score)		5.1±.1 (176)	5.9±.3 (39)	p<0.05
Age of Onset(age)		20.8±.9 (165)	12.9±1.4 (34)	p<0.001
Sleep Paralysis				
Occurrence (% Yes)		72.9 (274/376)	72.7 (56/77)	
Severity[c] (score)		5±.3 (172)	6.2±.7 (45)	
Age of Onset (age)		21.1±0.9 (145)	14.8±(32)	p<0.001

[a, b, c] see Table 3† proportion of HLA positive subjects with a shorter duration of cataplectic attacks is greater than those who are HLA negative; χ^2 =10.8, p=0.02.‡ when the frequency of cataplexy is separated into two groups (at least once per week and at least once per month) a chi-square test shows a significant difference between the frequency of cataplectic attacks and HLA typing; χ2= 5.0, p=0.01

disturbed MSLT data. Of note was the finding that hallucinations were more frequently frightening for HLA positive subjects (Table 4).

Age of Onset of Narcolepsy Symptoms

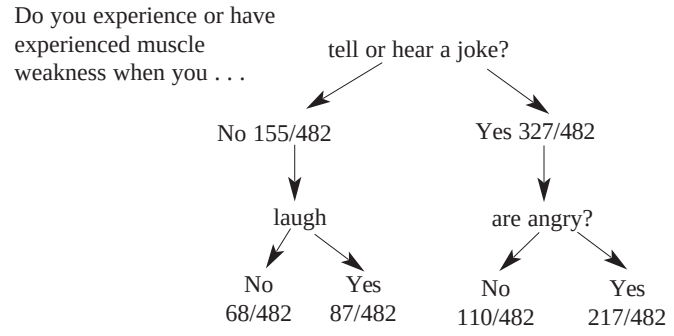
Self reported age of onset analysis is plotted in Figure 2. Sleepiness was usually the first symptom to occur, with mean age (19.20±0.45, n=469; mean ±SEM across all ethnic group), followed closely by hypnagogic hallucinations (19.50±0.77, n=211), sleep paralysis (20.11±0.74, n=189) and cataplexy (23.02±0.55, n=438). Age of onset differences were also plotted in reference to sleepiness onset (Figure 3 and 4). Interestingly, sleep paralysis and hypnagogic hallucinations (Fig. 4), but not cataplexy (Fig. 3), often preceded sleepiness.

Month of Birth Analysis

Birth months for all subjects were also compared with U.S. national center statistics data as described above (Figure 5). A non-significant increase in births was observed in the month of March (c2=2.3, OR=1.5 p=0.13), while narcoleptic subjects were less frequently born in September.

DISCUSSION

The primary aim of this study was to compare narcolepsy symptomatology across ethnic groups. We also used this large sample of patients to further describe the clinical picture, genetic, and natural history for this disorder. One of the most striking findings was the very similar report of symptomatology



Narcolepsy (482)	14%	18%	23%	45%
DQB1*0602+ (457)	56%	67%	93%	92%
Non Narcoleptic (920)	95%	2.9%	1.4%	0.3%

Figure 1—Cataplexy Trigger Decision Tree by HLA Typing. Cataplexy questions with the best sensitivity and specific values were previously selected using 983 subjects with various sleep disorders, including 63 with narcolepsy-cataplexy (see reference 5). The same analysis was subjected to our sample of 484 narcoleptic subjects and correlated with HLA typing. Note that approximately 2/3 of all narcoleptic patients answered that they experienced cataplexy triggered by joking with 92-93% HLA positivity. In contrast, only 1.7% of the non-narcoleptic population answered similarily (control data from reference 5).

and severity across ethnic groups. This finding confirms the biological homogeneity of the disorder across ethnicity. We were, however, surprised to find so few differences in the severity or the occurrence of specific symptoms. Differences in age and symptomatology severity could have been observed based on disparities in health care availability and/or access across ethnic groups. Similarly, sleep paralysis has been suggested to be more frequent in Asians and African Americans.[16-18] The prevalence of this symptom was, however, identical across ethnicity, even though generally more severe sleep paralysis was reported in these two ethnic groups.

Demographic aspects for the sample were consistent with previous studies with respect to the age of onset distribution (Fig. 2). Most patients developed cataplexy within four years following the onset of sleepiness (Fig. 3), while onset of sleep paralysis and hypnagogic hallucinations frequently occured before sleepiness commenced (Fig. 4). We also noted that most patients were slightly overweight relative to matched control values (Table 1). However, this effect was only marginally significant and of limited magnitude (106.6% over body weight). This effect is consistent with the previous reports[26-27] but of smaller magnitude, possibly because our sample was that of treated and generally adequately controlled narcoleptic subjects.

Birth month analysis revealed an increased number of nar-

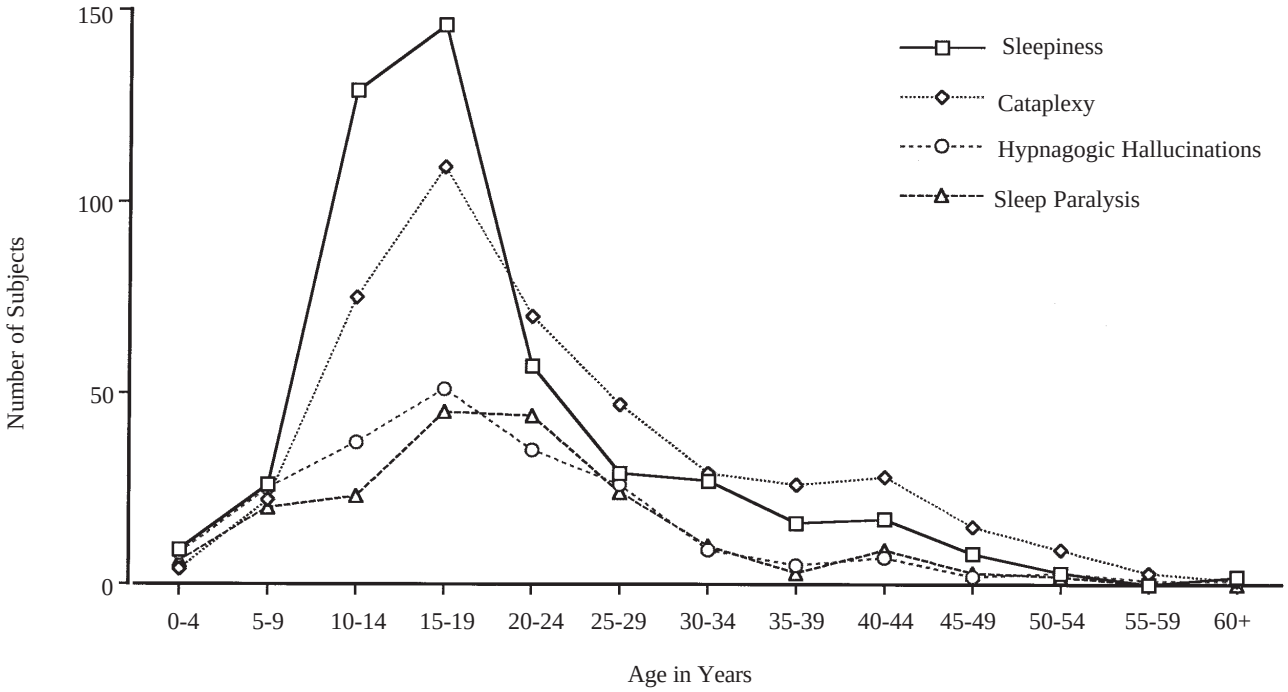


Figure 2—Age of onset of sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis in 469, 438, 210 and 189 patients, respectively. Self-reported age of for various narcolepsy symptoms was extracted from the Stanford Center for Narcolepsy Sleep Inventory. The number of subjects with onset at each age range is plotted. Note that sleepiness onset is generally earlier than the other symptoms.

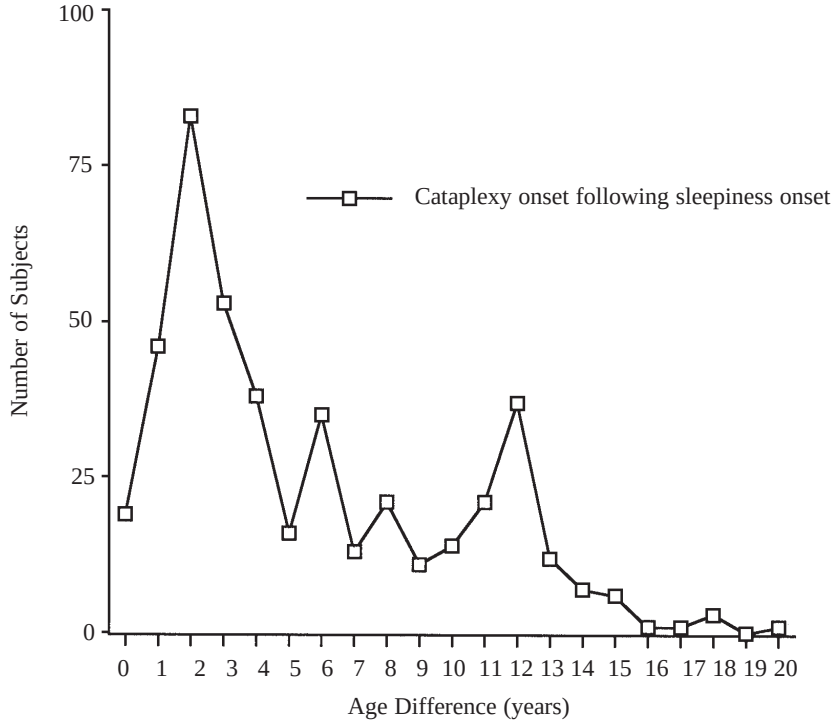


Figure 3—Cataplexy onset in reference to sleepiness onset. The difference between self-reported onset for sleepiness and cataplexy was calculated for each subject and plotted. Note that all subjects reported cataplexy occurring later than sleepiness, most often within 4 years but occasionally up to 20 years later.

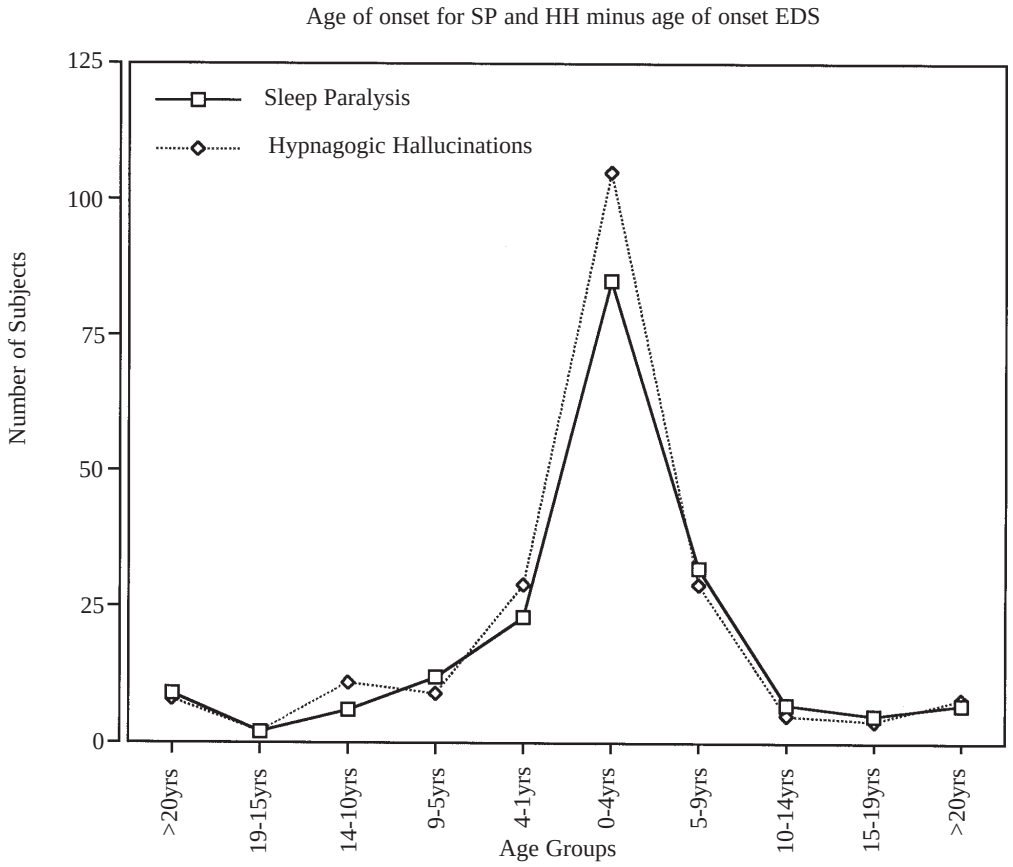


Figure 4—Sleep paralysis and hypnagogic hallucinations onset in reference to sleepiness onset. Differences were calculated as detailed in Figure 3. Note that as many subjects reported starting these symptoms before and after sleepiness onset.

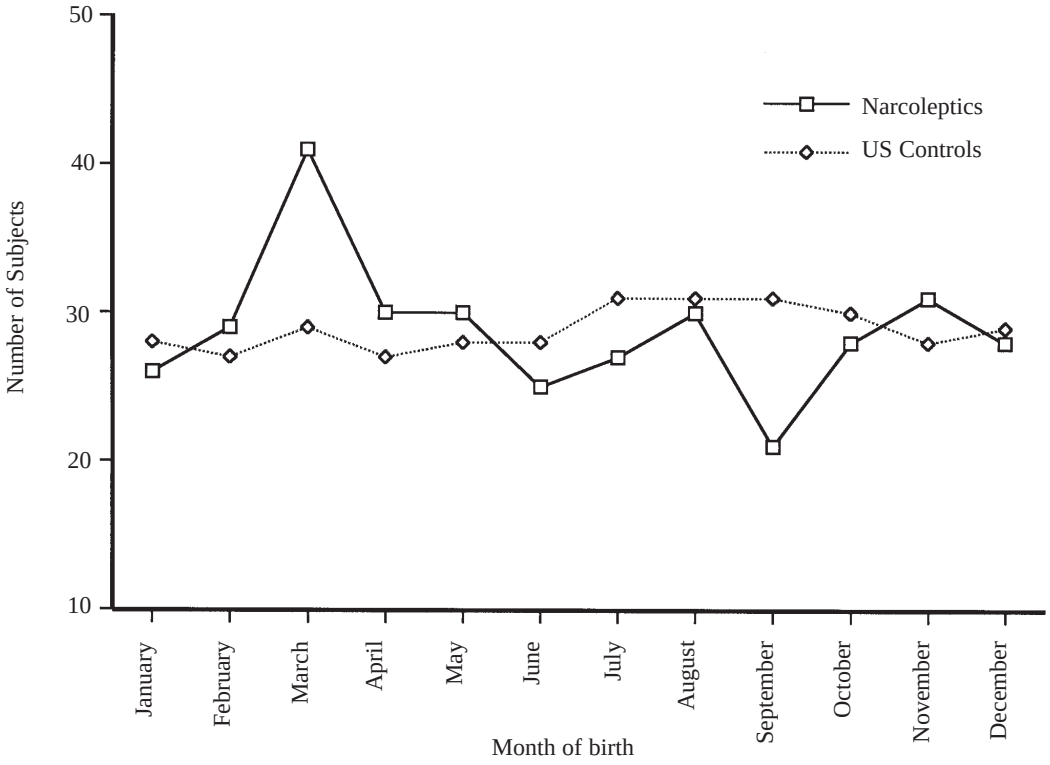


Figure 5—Birth month of narcoleptic subjects in comparison to control data. For detailed analysis, see method section. Note excess of births in the month of March for Narcoleptic subjects.

coleptic subjects born in the month of March (15% above average). A previous study had shown increased births in this exact same month in a sample of French and Canadian narcoleptic subjects.[28] Similar deviations from control data have been reported in other diseases,[29] most notably multiple sclerosis, a disease associated with a similar HLA type. These studies suggest perinatal influences in narcolepsy. Additional examinations in HLA positive controls and in other narcolepsy populations are needed to confirm this finding.

One of the most interesting aspects of this study was the tight correlation between HLA-DQB1*0602 positivity and the core symptomatology of narcolepsy, especially with regard to cataplexy. HLA positive subjects were generally older, with earlier onset of symptoms, as well as more severe and typical symptoms in terms of cataplexy, sleepiness, disturbed nocturnal sleep and polysomnographic features. This was, however, not the case for sleep paralysis and hypnagogic hallucinations, a result emphasizing again the lack of specificity of these two symptoms for the diagnosis of narcolepsy. We also found a surprisingly high correlation between our validated cataplexy decision tree and HLA positivity. An amazing 92-93% of patients with cataplexy triggered by joking were HLA-DQB1*0602 positive, making this question highly specific for defining genuine cataplexy in narcolepsy. Together with recent studies indicating a high degree of hypocretin deficiency in HLA positive patients with typical cataplexy,[10] these results indicate striking etiological and clinical homogeneity when cataplexy is narrowly defined. We believe this cataplexy question may be very useful to use in further epidemiological and research studies.

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