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DRB1*1502-DQB1*0601-DQA1*0103 and DRB1*04-DQB1*0302 in Jewish hypersomnolent patients

Nir Peled[a,*], Avraham Amar[b], Eli Peled[a], Chaim Brautbar[b], Giora Pillar[a]

[a]*Sleep Laboratory, Faculty of Medicine, Gutwirth Building, Technion – Israel Institute of Technology, Haifa 32000, Israel*
[b]*Tissue Typing Unit, Hebrew University – Hadassah Medical Organization, Jerusalem, Israel*

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Abstract

Objectives: Narcolepsy is a sleep disorder with a genetic association with the haplotype DRB1*1501, DQA1*0102, DQB1*0602. This haplotype has been described in different ethnic groups suffering from narcolepsy (Japanese, Caucasian, African Americans, Jews). In a recent study we have found the haplotype DRB1*1502, DQB1*0601, DQA1*0103 in three patients with hypersomnolence. The similarity of this haplotype to the narcoleptic haplotype DRB1*1501, DQB1*0602 and DQA1*0102 has raised the question of whether this haplotype is a marker for sleepiness, or rather indicates a variant of non-cataplectic narcolepsy. This study was conducted to further investigate this question.

Methods: HLA-DNA analysis was carried out in 20 healthy Jewish patients (age 23.9 ± 6.3 years; 13 Ashkenazi, seven non-Ashkenazi) who had objective measures of hypersomnolence. All underwent whole-night polysomnography, multiple sleep latency test and tissue typing.

Results: HLA-DNA analysis revealed HLA-DR2 in eight patients of whom five (25%) carried the haplotype DRB1*1502, DQB1*0601, DQA1*0103 (vs. 1.4% in the Israeli population, $P < 0.0001$). Six patients were diagnosed as non-cataplectic narcoleptics. Five of them carried the haplotype DRB1*1502, DQB1*0601, DQA1*0103. Forty percent of the patients carried the haplotype DRB1*04, DQB1*0302, which was not statistically different from its prevalence in the healthy Israeli population (25%).

Conclusions: This is the first report describing the haplotype DRB1*1502, DQB1*0601, DQA1*0103 in narcoleptic patients (non-cataplectic). This haplotype is close but different from the already known narcoleptic haplotype DRB1*1501, DQA1*0102, DQB1*0602. We assume that this haplotype represents a variant of non-cataplectic narcolepsy rather than association with hypersomnolence. However, in order to conclude whether this haplotype is a marker for the lack of cataplexy, or represents a variant of non-cataplectic narcolepsy, a larger group of patients should be investigated.

Keywords: HLA-DNA analysis; Hypersomnolence; Jews; Narcolepsy

1. Introduction

Narcolepsy is a sleep disorder characterized by a familial tendency, manifested classically by a tetrad of cataplexy, hypnagogic hallucination, sleep paralysis and autonomic behavior [1,2]. Since 1983, narcolepsy has been shown to be associated with tissue antigen HLA-DR2 [3]. At the gene level, the disease is associated with the haplotype DRB1*1501, DQA1*0102, DQB1*0602, which are in linkage disequilibrium. In a previous study we reported that the haplotype DRB1*1501, DQA1*0102, DQB1*0602 occurs in Jewish narcoleptics [4]. In the same study, a different haplotype DRB1*1502, DQB1*0601, DQA1*0103 was found in three other patients. Therefore, in order to investigate the occurrence of this latter haplotype in hypersomnolence patients, we investigated a group of 20 hypersomno-lence patients for tissue typing.

2. Methods

2.1. Subjects

Twenty patients (age 23.9 ± 6.3 years), 13 Ashkenazi, seven non-Ashkenazi (three of Yemenite origin) out of 200 patients, who were referred to the sleep laboratory because of daytime hypersomnolence unrelated to breathing or other disorders in sleep, participated in the study. All were healthy and did not take any medication. All were interviewed by a psychologist for mood and personality disorder, and kept a sleep diary, to exclude any inadequate sleep duration or sleep

* Corresponding author. Tel.: +972-4-8226730; fax: +972-4-8323045.
E-mail address: peledbn@inter.net.il (N. Peled).

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hygiene disturbances. Entering criteria were lack of any major disease, normal nocturnal polysomnography (without evidence of sleep apnea syndrome, multiple awakenings, periodic leg movements, etc.) and daytime hypersomnia with a mean sleep latency of less than 10 min on the multiple sleep latency test (MSLT). Head injuries and mood or stress disorders were reasons for excluding patients from the study. Out of the 50 patients who finally entered the study, 20 agreed to undergo tissue typing.

2.2. Sleep study and MSLT

All patients underwent a whole-night polysomnography that consisted of horizontal EOG, submental EMG, ECG, EEG (C3-A2), air flow (thermistor), chest movements, bed movements, and pulse oxymetry (ear/finger tip). All channels were displayed on a Nihon Kohden polygraph (EEG-4214). Bedtime was between 23:00 and 07:00 h. The MSLT was conducted according to Carskadon et al.'s guidelines [5]. Scoring of the night and the MSLT recordings was done according to Rechtschaffen and Kales' criteria [6].

2.3. HLA-DNA analysis

HLA-DNA analysis was performed as described elsewhere [7–9].

3. Results

Twenty patients (age 23.9 ± 6.3 years) participated in the study. Their main complaints were prolonged nocturnal sleep, inability to stay awake in passive conditions, non-refreshing sleep attacks during the day, fatigue and performance disabilities. Symptoms had started 4.9 ± 2.3 years before the study. The clinical and objective findings of all patients are detailed in Table 1. None had cataplexy and none used medications or stimulants. Five reported hypnagogic hallucinations, and three of them also had sleep paralysis.

A nocturnal sleep study revealed a mean sleep latency of 10.4 ± 9.9 min, a REM latency of 68.5 ± 38.1 min, and a sleep efficiency of 92.3 ± 3.6%. Two patients had a nocturnal sleep onset REM period (14 and 15 min). On MSLT, all patients (except two who fell asleep only four times) fell asleep during all five attempts with a mean sleep latency of 5.3 ± 2.0 min; 10 had a mean sleep latency of <5 min. REM sleep appeared in 2.7 ± 1.4 of the five MSLT trials; 16 patients had two or more REMs on MSLT. The patients with hypnagogic hallucination ($N = 5$) tended to have shorter REM latency (53.2 ± 16.2 vs. 73.6 ± 42.3 min, NS). The patients with a nocturnal sleep onset REM period did not differ in any way from the rest of the patients. The first four patients were diagnosed as non-cataplectic narcoleptics (Table 1), the patients with less than two REMs on MSLT were diagnosed as 'idiopathic hypersomniacs' and the others were diagnosed as 'hypersomniacs not otherwise

Table 1
Clinical, polysomnographic and gene typing data of all 20 patients[a]

Patient	Age (years)	Hyp. hall.	Sleep paralysis	Nocturnal sleep onset	Nocturnal REM latency	Sleep efficiency	MSLT sleep latency	MSLT REMs	DR	DRB1	DRB1	DQB1	DQB1
V.N.*	18.5	1	1	5	79	93	4.8	3	01-07	01	07	02	0502
L.O.*	28	1	0	10	47	88	9.4	3	02-02	1502	1502	0601	0601
G.S.*	26	1	1	13	58	92	4.0	4	02-11	1502	1104	0301	0601
K.O.*	38	1	0	3	38	94	9.0	2	02-04	1502	0404	0402	0601
M.S.**	33	0	0	2	14	94	4.8	2	02-07	1502	0701	0201	0601
R.A.**	26	0	0	12	47	87	5.8	4	02-07	1502	07	02	0601
V.A.§	19.5	0	0	7	70	98	4.0	5	01-11	01	11	0301	0501
Y.S.§	21	0	0	10	108	95	6.4	5	04-13	04	13	0302	0604
L.A.§	21	0	0	12	15	92	4.4	5	11-11	11	11	0301	0301
L.G.§	21	0	0	12	171	93	2.6	3	01-11	01	11	0301	0501
S.O.§	20	0	0	25	52	93	7.2	3	04-11	04	11	0301	0302
S.I.§	21	0	0	44	29	88	4.4	3	04-11	04	11	0302	0603
B.G.§	19.5	0	0	0	77	99	1.8	2	04-04	04	04	0302	0302
B.N.§	21	0	0	4	59	93	7.4	2	03-04	03	04	02	0302
S.E.§	23	0	0	6	77	91	2.8	2	01-01	01	04	0302	0501
A.T.§	18	0	0	13	82	88	5.6	2	02-04	1604	04	0302	0502
W.E.†	21	1	1	9	44	89	6.6	1	03-07	03	07	02	
O.A.†	40	0	0	8	92	87	5.4	1	02-07	1601	07	0303	0502
K.M.†	23.5	0	0	3	78	94	4.8	1	04-14	04	14	0302	0503
M.A.†	19.5	0	0	4	133	98	5.2	0	02-03	1601	03	02	0502
AVG	23.9			10.4	68.5	92.3	5.3	2.7					
STD	6.3			9.9	38.1	3.6	2.0	1.4					

[a] None of the patients had cataplexy. Hyp. hall., hypnagogic hallucination. *Narcoleptics; **see text; §hypersomnia not otherwise specified; †idiopathic hypersomnia.

specified'. Two patients (M.S. and R.A.), as will be discussed later, were diagnosed as narcoleptics.

Molecular analysis of HLA-DR2 revealed two subtypes: DRB1*15 and DRB1*16. Six and eight allelic variants have been defined so far in the DRB1*15 and the DRB1*16 subtypes, respectively. Of the 20 patients tested, eight were found to carry DR2(DRB1*15 or 16), with five (25%) carrying the haplotype DRB1*1502, DQB1*0601 (Table 1) which is frequent in 1.4% of the Jewish Israeli population ($\chi^2 = 50.69$, $P < 0.0001$) [10]. Three of these patients had narcolepsy (L.O., G.S., K.O.). The two others had a lack of clinical symptoms in order to be diagnosed as narcoleptics according to the international classification of sleep disorders (ICSD).

The haplotype DRB1*04-DQB1*0302 was the most prevalent in this patient group (40%), however, without a significant difference compared to its prevalence in the Israeli population (25%, $\chi^2 = 2.84$, R.R. = 2.62) [10]. The linkage of DRB1*04 was previously reported to be in disequilibrium with DQB1*0302 [11].

In order to differentiate between the patients carrying the haplotype DRB1*1502, DQB1*0601 (group A, $N = 5$), we compared their clinical data to the rest of the patients (group B). Age (A: 30.2 ± 5.2 vs. B: 21.8 ± 5.2 years; $P = 0.006$) was significantly different between the groups. REM latency was 40.8 ± 16.6 min in group A, and 77.7 ± 39.1 min in group B ($P = 0.058$). Hypnagogic hallucinations were reported in 3/5 patients in group A compared to 2/15 in group B (NS). Daily sleep attacks occurred 2.3 ± 2.1 times in group A compared to 1.3 ± 1.5 times in group B ($P = 0.07$). All other nocturnal and MSLT results were almost identical.

The same analysis was carried out in the group carrying the allele DRB1*04 ($N = 8$), but no significant differences were observed.

4. Discussion

This study suggests that HLA-DR2 with the haplotype DRB1*1502, DQB1*0601 and DQA1*0103 might be carried by a subgroup of non-cataplectic narcoleptic patients. These alleles are different but close to the already known narcoleptic haplotype DRB1*1501, DQB1*0602 and DQA1*0102. Discussing our results, we can focus on two issues: (1) clinical difficulties in diagnosing non-cataplectic narcolepsy; and (2) possible interpretations of our DNA findings.

Severe excessive daytime sleepiness as presented by our patients may be a presenting symptom of narcolepsy although complete manifestation of the narcolepsy tetrada (cataplexy, hypnagogic hallucination, sleep paralysis and automatic behavior) may occur years after the initial diagnosis [2,12,13]. In the case of non-cataplectic narcolepsy, there may be confusion with other sleep disorders associated with hypersomnolence [14].

Cataplexy was described first by Gelineau in 1880 [15] as a part of the classical narcoleptic appearance. However, the question of whether cataplexy is essential for the diagnosis of narcolepsy has been controversial for many years, mainly due to the often reported time lag between the first appearance of daytime sleepiness and cataplexy. Approximately one-third of patients complaining of excessive daytime sleepiness and having abnormally short REM latency do not have cataplexy. These patients have fewer daytime naps and less REM sleep in comparison with patients with cataplexy [16]. However, non-cataplectic narcolepsy is believed to be a subgroup of narcolepsy, since both have the same epidemiological and familial characteristics and, moreover, because some patients developed cataplexy many years after the first appearance of daytime sleepiness [2]. In our group, four patients had narcolepsy according to the ICSD (patients V.N., L.O., G.S., K.O., Table 1). Three of them carried the genetic haplotype DRB1*1502, DQB1*0601 and DQA1*0103. Hence, this is the first time this haplotype has been described in narcoleptic patients.

The association of narcolepsy with HLA-DR2 and HLA-DQw1 has been previously described [17]. Primarily, in 1983, 100% of the Japanese with narcolepsy were found to carry HLA-DR2 [3]. Since then, similar findings have been found in different ethnic groups with narcolepsy [18]. The haplotype found in 95–100% of the Caucasian and Japanese narcoleptics with cataplexy has the serologic specificities HLA-DR15 (DR2), DQ6(DQ1) [19]. At the gene level, it was found to correspond to DRB1*1501, DQA1*0102, DQB1*0602, also in Jewish narcoleptics [4]. In African Americans, predisposition to narcolepsy is more closely associated with DQB1*0602 than with DRB1*1501 [20]. Our finding of a new haplotype associated with narcolepsy raises several questions. Is it a subgroup of narcolepsy? Is it a subgroup of non-cataplectic narcolepsy? Is cataplexy associated with the difference between the two haplotypes? However, in order to answer these questions, a larger group of patients with non-cataplectic narcolepsy should be investigated.

Two additional patients carried the haplotype DRB1*1502, DQB1*0601 and DQA1*0103 (patients M.S. and R.A., Table 1). They did not fit the minimal criteria for narcolepsy as was determined by the ICSD, even though patient M.S. had a nocturnal REM latency of 14 min. Both of them lacked D criteria (ICSD-associated features) [1] in order to be considered as narcoleptics. Neither could we find any 'excuse' to separate them from the other patients who did not carry the genetic haplotype DRB1*1502, DQB1*0601, DQA1*0103. Since this haplotype is uncommon in Jews [10], and there are no data to support the existence of such a haplotype in other hypersomnolence situations, we speculated whether these patients suffer from narcolepsy, although do not yet fit the ICSD definition. If so, five out of six non-cataplectic narcoleptic patients carried the genetic haplotype DRB1*1502, DQB1*0601, DQA1*0103.

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