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HLA Subtype Distribution in Central Disorders of Hypersomnolence and Relationship of HLA Typing with Clinical and Electrophysiological Findings in Patients with Excessive Daytime Sleepiness

Hipersomnolansın Santral Bozukluklarında HLA Alttiplerinin Dağılımı ve Gündüz Aşırı Uykululuk Yakınması Olan Hastalarda HLA Tiplendirmesinin Klinik ve Elektrofizyolojik Bulgularla İlişkisi

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Abstract

Objective: Human leukocyte antigens (HLA antigens) provides important data on differential diagnosis of central disorders of hypersomnolence (CDH). While the relation of narcolepsy type-1 (NT1) with autoimmunity has been well-characterized by HLAs, the literature on other types of CDH is insufficient. This study aims to reveal HLA antigens subtypes in the whole spectrum of CDH, and explore their association with objective sleep measures.

Materials and Methods: Patients who complained of excessive daytime sleepiness and underwent HLA antigens typing were analyzed. Demographics, anthropometrics, sleep-related complaints, polysomnography, and multiple sleep latency test parameters were documented. The frequency of HLA antigens phenotypes was compared between CDH subtypes, and it was analyzed for sleep-related clinical and electrophysiological features.

Results: Eighty-two participants were included [median age: 37.0 (17.0-66.0), 62.5% female], of whom 80 reached a final diagnosis of hypersomnolence (31 narcolepsy, 25 non-narcolepsy CDH and 24 non-central hypersomnia). The most common HLA antigens subtype in the whole population was DQB1*03 (95.1%). DQB1*06 was more frequent in NT1 compared to other groups (p<0.001), while DQB1*02 was more commonly seen in non-narcolepsy cases (p<0.001). The clinical and polysomnographic features that were specific to narcolepsy were more frequent in the presence of DQB1*06 and, in the absence of DQB1*02 and DQB1*05.

Öz

Amaç: İnsan lökosit antijeni (HLA) hipersomnolansın santral bozukluklarının tanısal değerlendirilmesinde önemli veriler sunmaktadır. Narkolepsi tip 1 (NT1) ile otoimmünite ilişkisi HLA tiplendirmesi üzerinden halihazırda gösterilmişken, hipersomnolansın santral bozukluklarının diğer türleriyle ilgili veriler sınırlıdır. Bu çalışmanın amacı, hipersomnolansın santral bozuklukları spektrumundaki HLA alt tiplerini ve bu alt tiplerin objektif uyku parametreleriyle ilişkisini araştırmaktır.

Gereç ve Yöntem: Çalışmaya gündüz aşırı gündüz uykululuk şikayetiyle uyku laboratuvarına başvuran ve HLA tiplendirmesi yapılan hastalar dahil edilmiştir. Hastaların demografik bilgileri, antropometrik verileri, uyku yakınmaları, polisomnografi ve çoklu uyku latans testi parametreleri kaydedilmiştir. HLA alt tiplerinin sıklığı farklı hipersomni alt grupları arasında karşılaştırılmış ve hastaların klinik ve elektrofizyolojik verileriyle birlikte analiz edilmiştir.

Bulgular: Çalışmaya 82 katılımcı dahil edilmiş [ortanca yaş: 37,0 (17,0-66,0), %62,5 kadın], bu hastalardan 80'i nihai tanı alabilmiştir (31 narkolepsi, 25 narkolepsi-dışı santral hipersomni ve 24 santral-olmayan hipersomni). Tüm çalışma popülasyonunda en yaygın HLA alt tipi DQB1*03 olarak saptanmıştır (%95,1). NT1 olgularında diğer gruplara kıyasla DQB1*06 anlamlı olarak daha sık görülürken (p<0,001), DQB1*02 ise narkolepsi-dışı hipersomnilerde daha yaygındır (p<0,001). Narkolepsiye özgü klinik ve polisomnografik özellikler DQB1*06'nın varlığında ve DQB1*02 ile DQB1*05'in yokluğunda daha sık pozitif bulunmuştur.

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Conclusion: This study not only showed the power of DQB1*06 to differentiate NT1 from non-NT1, in line with existing literature; also revealed importance of DQB1*03 as a potent common marker of hypersomnolence and DQB1*02 as more frequent in non-narcolepsy CDH. These observations will enable more comprehensive analyses as the study population increases and diversifies.

Keywords: Disorders of excessive somnolence, human leukocyte antigen, HLA antigens, autoimmunity

Sonuç: Bu çalışma mevcut literatür verileriyle uyumlu olarak DQB1*06'nın NT1 olgularını, NT1-dışı hipersomnilerden ayırt etme gücünü göstermiştir. Ayrıca hipersomni için güçlü bir ortak belirteç olarak DQB1*03'ün ve narkolepsi-dışı hipersomnilerde daha sık görülen DQB1*02'nin tanısal önemini ortaya koymuştur. Bu gözlemler, çalışma popülasyonu ve çeşitliliği arttıkça daha kapsamlı analizlere olanak tanıyacaktır.

Anahtar Kelimeler: Aşırı uyku halinin bozuklukları, insan lökositantijeni (HLA) antijenleri, otoimmunite

Introduction

Central disorders of hypersomnolence (CDH) are a group of sleep disorders characterised by excessive daytime sleepiness (EDS), which refers to being sleepy during the day when one should remain awake and alert, and/or hypersomnia, which refers to increased sleep duration at night.[1] An estimated 5% of the general population suffers from EDS and/or hypersomnolence, and in about 1-2% of the population, EDS/hypersomnolence is due to central causes, so-called CDH.[2] In the latest version of the International Classification of Sleep Disorders published in 2023 (ICSD-3-TR), CDH is categorized under eight subheadings.[3] These are narcolepsy type-1 (NT1), narcolepsy type-2 (NT2), idiopathic hypersomnia (IH), Kleine-Levin syndrome, hypersomnia due to a medical disorder, hypersomnia due to a medication or substance, hypersomnia due to a mental disorder and insufficient sleep syndrome.[3] The diagnostic tools specified in the diagnostic criteria for differentiating the subtypes of CDH from each other and from other sleep disorders are mainly based on clinical history/anamnesis, full-night polysomnography (PSG) and multiple sleep latency test (MSLT), and for selected cases as an optional tool, the measurement of hypocretin level in cerebrospinal fluid. However, in clinical practice, various other diagnostic instruments, e.g. subjective sleep assessment scales, ambulatory sleep monitoring, and human leukocyte antigens (HLA antigens) typing are frequently used in the differential diagnosis processes.[4]

The close association of the HLA antigens system, which comprises a gene complex responsible for encoding cell surface proteins that regulate immune system functions,[5] with the pathogenesis of NT1 has already been shown through large-scale population studies.[6,7] Among HLA antigens class II genes, DRB1*15:01, DQA1*01:02 and DQB1*06:02 are the most common disease-associated haplotypes in narcolepsy.[8] More than 85% of patients with NT1 have HLA antigens DQB1*0602, often in combination with HLA antigens DRB1*1501, while only around 40% of the patients having narcolepsy without cataplexy have HLA antigens DQB1*0602 suggesting a strong genetic susceptibility for autoimmunity against hypocretin-producing neurons in NT1, whereas an increased pathogenetic heterogeneity in NT2.[9] Demonstration of these HLA antigens subtypes not only provides support for confirming the diagnosis of NT1 but may also predict the severity of clinical symptoms; for example, DQB1*0602 positivity has already been shown to be associated with increased frequency of naps and risk of accidents due to daytime sleepiness in NT1.[10] Therefore, HLA antigens typing has important implications in the clinical practice of narcolepsy. However, HLA antigens subtypes that may be used in the differential diagnosis of hypersomnolence subtypes apart from NT1, including all central and non-central causes of hypersomnolence, have not yet been demonstrated. This study aimed to document the relationships between HLA antigens class II genes and both the type of hypersomnolence diagnoses and the sleep-related clinical and electrophysiological features in a wide spectrum of patients presenting with EDS and/or hypersomnia. Based on the hypothesis that there are specific HLA antigens patterns encompassing different types of hypersomnolence, this study will provide a perspective on the associations between HLA antigens subtypes and various phenotypes of hypersomnolence with their specific clinical and electrophysiological findings.

Materials and Methods

This study was conducted with a retrospective design in the sleep and disorders units of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine and Aydın Adnan Menderes University, Faculty of Medicine, after the approval of the Ethics Committee of the İstanbul University-Cerrahpaşa (approval number: 15.11.2023-837477, date: 15.11.2023).

Participants

Among the patients who applied to the sleep clinic with complaints of EDS and/or hypersomnia in the last two years and who underwent PSG and MSLT examinations due to these complaints, those whose HLA antigens typing data could be accessed were retrospectively included in the study. Patients with systemic or neurologic diseases or comorbid sleep disorders that may cause EDS and/or hypersomnia were excluded from the study. Informed consent had been obtained from all the study participants to get an allowance to investigate past medical records.

Diagnostic Work-up for EDS/Hypersomnolence

After the recording of routine demographic and anthropometric parameters, baseline Epworth Sleepiness scale scores[11] of all study participants at the time of the hypersomnolence diagnosis were documented. Also, the presence of narcolepsy-specific clinical complaints, e.g. cataplexy, hypnogogic/hypnapompic hallucinations and sleep paralysis and a history of REM (rapid eye movements) sleep behaviour disorder (RBD) attacks, were noted. All participants were evaluated with a full-night video-PSG at Sleep Laboratory [American Academy of Sleep Medicine (AASM) type 1] and MSLT after the PSG night. The recording and scoring of sleep and associated events were performed

according to the on-time AASM Manual for the Scoring of Sleep and Associated Events.[12,13] The following parameters were evaluated in full-night PSG: Total sleep time (minutes), sleep efficiency (percent), wakefulness after sleep onset (WASO, minutes), sleep and REM-sleep latency (minutes), distribution of sleep stages N1, N2, N3 and REM (percent), apnea-hypopnea index (AHI/hour), periodic limb movements index (/hour), REM sleep without atonia (RWA, present/absent), sleep onset REM (SOREM, present/absent); whereas sleep latency and number of SOREMs were documented from MSLT recordings. According to the results of subjective and objective sleep assessment, and in line with the diagnostic criteria in the 3rd edition-text revision of the International classification of sleep disorders,[3] the study participants were grouped as (1) NT1, (2) NT2, (3) IH, (4) other (5) CDH residual hypersomnia after positive airway pressure therapy in obstructive sleep apnea (RH) and (6) non-central disorders of hypersomnolence (non-CDH), which was characterised by the presence of subjective sleepiness, but lack of any objective evidence of CDH or insufficient fulfil of CDH diagnostic criteria.

HLA Antigens Typing

The isolation of the DNA from blood samples was conducted using BioRobot EZ1 and an EZ-DNA extraction kit (Qiagen-Germany). HLA antigens typing at 2 digits of HLA-A, HLA-B, HLA-C and HLA-DQ alleles was determined with Luminex 100/200 Instrument that uses sequence-specific oligonucleotide probes bound to color-coded microbeads for identification of HLA antigens alleles (Luminex Corp., USA). LIFECODES SSO Typing kits were used for the HLA antigens typing (Lifecodes, Immucor, Germany). These tests are reverse sequence-specific oligonucleotide DNA typing assays in which SSO (Sequence-Specific Oligonucleotide) probes and color-coded microspheres are used in order to identify HLA antigens alleles. Polymerase chain reaction mixture included 15 µL of the Lifecodes Master Mix (Immucor), 200 ng of genomic DNA, and 2.5 U Taq polymerase for a 50 µL final volume. The patterns were compared with the common and well-documented HLA antigens alleles Probe Hit Tables (IMGT/HLA antigens Sequence Database Release 3.11.0) by using the MatchIT DNA program (Immucor). Further details regarding the molecular cycles and sample processing were presented in a previous article; see Kocak et al.[14]

Statistical Analysis

IBM SPSS Statistics Data Editor 26.0 and RStudio IDE 2022.07.0 were used for the statistical analysis and data visualization. Categorical data was shown as n (%), whereas continuous data was shown as median (minimum-maximum). After determining the non-parametric distribution of the dataset by the Shapiro-Wilk test, the chi-square test was used for the categorical data, and the Mann-Whitney-U test and Kruskal-Wallis tests were used for the continuous data to perform group comparisons. Post-hoc analysis was performed using a pairwise Z-test for categorical data and a Dunn test for continuous data. A p-value equal to or lower than 0.05 was accepted as statistically significant. Based on the sample size calculation with G*power 3.1.9.7 with reference to the study by Han et al.[15] comparing the incidence of DQB1*0602 carriage in NT1 and NT2 cases, when type I error (α)=0.05, power (1-β)=0.95, effect size d=0.66 and the alternative hypothesis is two-way, it was planned to include at least 75 participants to reach a significant difference between the groups and a total of 82 participants were included. Firstly, the HLA antigens phenotype distribution among the main groups and subgroups of hypersomnolence diagnosis were compared. Then, the objective sleep assessment parameters were compared among the HLA antigens positive vs negative groups for certain and most frequent HLA antigens phenotypes, overall, to reveal the relationship between HLA antigens phenotypes and different types of hypersomnolence both regarding the final diagnoses and their objective sleep characteristics.

Results

Eighty-two participants were included to the study, with the median age of 37.0 (17.0-66.0) and a female dominance 62.5%, of which 80 reached a final diagnosis of hypersomnolence. The general diagnosis distribution was 31 patients with narcolepsy, 25 patients with non-narcolepsy CDH and 24 patients with non-CDH. More specifically, NT1 group composed of 25 patients, NT2 group 6 patients, IH group 14 patients, other CDH group 3 patients, RH group 6 patients and non-CDH 24 patients. In the whole group, the median sleep latency in nighttime sleep was 8.4 minutes with 25.3% SOREM, whereas the median sleep latency in MSLT was 6.8 minutes with a median of 0.5 SOREM count. The most common HLA antigens subtype in the whole population was DQB1*03 (95.1%), followed by DQB1*05 (76.5%) and DQA1*01 (73.3%), see Table 1. The most common HLA antigens subtype, DQB1*03, was also the most evenly distributed allel among different types of hypersomnolence diagnosis (92.0% in narcolepsy, 95.0% in non-narcolepsy CDH and 100% in non-CDH group), suggests

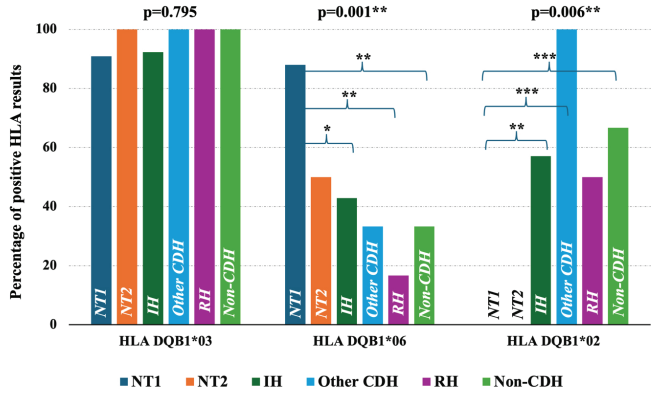

Figure 1. The percentage distribution of HLA DQB1*03, HLA DQB1*06 and HLA DQB1*02 positive patients, respectively, categorized by different types of hypersomnolence.
CDH: Central disorders of hypersomnolence, IH: Idiopathic hypersomnia, NT1: Narcolepsy type-1, NT2: Narcolepsy type-2, RH: Residual hypersomnia

Table 1. The comparison of different HLA phenotypes among (1) general groups, and (2) subgroups of hypersomnolence diagnosis

HLA Subtypes and general distribution			Hypersomnolence groups					Hypersomnolence subgroups						
HLA phenotypes positivity	n of HLA results	n of positive HLA results	Overall (n=80)	Narcolepsy (n=31)	Non-narcolep y CDH (n=25)	Non-CDH hypersomnia (n=24)	Test statistics	p	NT1 (n=25)	NT2 (n=6)	IH (n=14)	Other CDH (n=3)	RH (n=6)	Non-CDH (n=24)	Test statistics	p
DQB1*03 (%)	61	58	95.1	92.0	95.0	100.0	1.336	0.513	90.9	100.0	92.3	100.0	100.0	100.0	2.378	0.795
DQB1*05 (%)	34	26	76.5	60.0	90.9	83.3	3.507	0.173	57.1	100.0	83.3	100.0	100.0	83.3	4.825	0.438
DQA1*01 (%)	15	11	73.3	72.7	66.7	100.0	0.434	0.805	72.7	0	50.0	0	100.0	100.0	1.286	0.732
DRB1*04 (%)	13	7	53.8	63.6	0	0	2.758	0.252	63.6	0	0	0	0	0	2.758	0.252
DQA1*03 (%)	15	8	53.3	63.6	33.3	0	2.094	0.351	63.6	0	0	0	100.0	0	4.773	0.189
DQB1*06 (%)	78	41	52.6	**80.6a**	**34.8b**	**33.3b**	**17.191**	**<0.001*** **	**88.0a**	**50.0a,b**	**42.9b**	**33.3a,b**	**16.7b**	**33.3b**	**20.240**	**0.001****
DRB1*15 (%)	12	6	50.0	40.0	100.0	100.0	2.400	0.301	40.0	0	100.0	0	0	100.0	2.400	0.301
DQA1*05 (%)	15	6	40.0	36.4	33.3	100.0	1.616	0.446	36.4	0	50.0	0	0	100.0	2.311	0.510
DRB1*11 (%)	13	5	38.5	36.4	0	100.0	2.245	0.325	36.4	0	0	0	0	38.5	2.245	0.325
DQB1*02 (%)	38	14	36.8	**0a**	**60.0b**	**66.7b**	**15.459**	**<0.001*** **	**0a**	**0a,b**	**57.1b**	**100.0b**	**50.0a,b**	**66.7b**	**16.248**	**0.006****
DRB1*01 (%)	13	4	30.8	36.4	0	0	1.051	0.591	36.4	0	0	0	0	0	1.051	0.591
DRB1*14 (%)	13	2	15.4	18.2	0	0	0.430	0.807	18.2	0	0	0	0	0	0.430	0.807
DRB1*16 (%)	13	1	7.7	0	100.0	0			0	0	100.0	0	0	0		
DQA1*02 (%)	15	1	6.7	0	33.3	0			0	0	50.0	0	0	0		
DQB1*04 (%)	16	1	6.3	0	0	50.0			0	0	0	0	0	50.0		
DQB1*08 (%)	21	0	0.0	0	0	0			0	0	0	0	0	0		

The values that were designated with different letter in each row were significantly different from each other in pairwise group comparison. Chi-square test was used for categorical group comparisons of percentages. Significant results was demonstrated in bold. p<0.05*, p<0.01**, p<0.001***,

CDH: Central disorders of hypersomnolence, HLA: Human leukocyte antigen, IH: Idiopathic hypersomnia, NT1: Narcolepsy type-1, NT2: Narcolepsy type-2, RH: Residual hypersomnia

being a common marker of hypersomnolence. DQB1*06 was significantly more frequent in NT1 compared to IH, RH and non-CDH groups (p=0.001), whereas the presence of DQB1*02 subtype in IH, other-CDH and non-CDH groups, compared to NT1 was statistically significant (p=0.006), see Figure 1. In other words, the high frequency of DQB1*6 and the absence of DQB1*02 in narcolepsy cases were significantly different from non-narcolepsy CDH and non-CDH groups (p<0.001). Regarding the relationship between subjective or objective sleep assessment parameters and HLA antigens subtype distribution, the most prominent finding was that clinical and polysomnographical features which were known to be specific for narcolepsy were more frequent in presence of DQB1*06 and, in absence of DQB1*05 and DQB1*02. REM latency in nighttime PSG was shorter in DQB1*06 positive subjects compared to negative ones (p=0.002) and longer in DQB1*05 positive subjects compared to negative ones (p=0.017). The percent of positive SOREM in nighttime sleep was higher in DQB1*06 positive subjects compared to negative ones and in DQB1*05 and DQB1*02 negative subjects compared to positive ones (p=0.001). The same group differences were also observed for the SOREM count in MSLT (Table 2). Sleep latency in MSLT was significantly shorter DQB1*06 positive subjects compared to negative ones (p=0.007) and longer in DQB1*02 positive subjects compared to negative ones (p=0.002). The clinical parameters, that were questioned specifically as the narcolepsy-specific complaints like cataplexy, sleep paralysis and hypnogogic/hypnapompic hallucinations were more frequent in DQB1*06 positive and DQB1*02-DQB1*05 negative subjects. The comparison analysis, conducted for the positivity vs. negativity of other HLA-DQ and HLA-DR phenotypes listed in Table 1, in relation to subjective or objective sleep assessment parameters did not reveal any significant difference.

Discussion

This study demonstrated the reliability of DQB1*06 to differentiate narcolepsy, more specifically NT1, from other types of hypersomnolences in line with existing literature. Moreover, it revealed a subtype as DQB1*03, which was similarly distributed in different types of hypersomnolence as a potent common marker of EDS/hypersomnia. Last but not least, DQB1*02 and DQB1*05 subtypes

Table 2. The comparison of demographical and sleep-related features among different HLA phenotypes (HLA DQB1*06, *05 and *02) in all study population

			HLA DQB1*06				HLA DQB1*05				HLA DQB1*02			
	Overall (n=82)	**Test type**	**HLA DQB1*06 (+), n=41**	**HLA DQB1*06 (-), n=37**	**Test statistics**	**p**	**HLA DQB1*05 (+), n=26**	**HLA DQB1*05 (-), n=8**	**Test statistics**	**p**	**HLA DQB1*02 (+), n=14**	**HLA DQB1*02 (-), n=24**	**Test statistics**	**p**
Age, years	37.0 (17.0-66.0)	Mann-Whitney-U	37.0 (18.0-57.0)	37.0 (17.0-66.0)	802.0	0.981	39.0 (17.0-57.0)	38.0 (22.0-50.0)	118.0	0.591	35.0 (18.0-52.0)	36.0 (20.0-57.0)	191.0	0.501
Gender, female, %	62.5	Chi-square	68.3	56.4	0.750	0.386	61.5	62.5	0.002	0.961	28.6a	66.7b	5.147	0.023*
Body-mass index, kg/m^2	27.3 (15.6-47.6)	Mann-Whitney-U	27.8 (15.6-44.1)	26.7 (17.5-47.6)	883.0	0.422	27.0 (17.5-39.5)	29.7 (22.3-44.1)	83.0	0.413	27.7 (22.8-36.0)	27.7 (19.4-44.1)	174.0	0.870
Total sleep time, minutes	420.5 (261.0-552.0)	Mann-Whitney-U	435.7 (299.5-545.5)	412.0 (261.0-552.0)	894.5	0.261	429.0 (329.5-545.5)	433.5 (315.0-506.0)	107.5	0.889	410.5 (327.0-541.0)	434.0 (299.5-509.0)	132.5	0.287
Sleep latency, minutes	8.4 (0-240.0)	Mann-Whitney-U	6.9 (0-240.0)	10.4 (0.2-90.0)	649.0	0.199	7.5 (0.2-86.0)	8.9 (0-59.3)	104.5	1.000	17.5 (4.4)	11.0 (0-240.0)	203.5	0.287
REM latency, minutes	88.7 (0-469.3)	Mann-Whitney-U	67.0 (0-322.0)	115.9 (1.3-469.3)	444.5	0.002**	101.9 (0-285.0)	8.7 (2.0-119.3)	162.0	0.017*	83.5 (3.0-278.5)	61.5 (0-391.0)	209.0	0.223
WASO, minutes	61.1 (6.1-479.1)	Mann-Whitney-U	62.9 (6.1-479.1)	59.5 (54.2-97.8)	713.0	0.511	52.6 (16.1-136.5)	52.8 (6.1-84.0)	117.0	0.618	64.7 (14.8-158.7)	60.7 (6.1-479.1)	201.0	0.330
Sleep efficiency, %	88.2 (46.6-97.8)	Mann-Whitney-U	88.2 (46.6-96.5)	87.8 (54.2-97.8)	860.0	0.433	89.2 (72.3-96.5)	89.9 (70.3-96.4)	101.5	0.921	87.4 (70.6-95.7)	89.0 (46.6-96.5)	143.5	0.463
RWA, yes, %	31.6	Chi-square	40.0	23.1	1.891	0.169	30.8	37.5	0.125	0.724	21.4	25.0	0.062	0.803
RBD, yes, %	17.5	Chi-square	19.5	15.4	0.037	0.848	11.5	37.5	2.506	0.113	14.3	16.7	0.038	0.846
SOREM in nighttime sleep, yes, %	25.3	Chi-square	42.5a	7.7b	13.272	0.001**	23.1a	87.5b	11.115	0.001**	0.0	54.2	11.527	0.001**
Sleep latency in MSLT, minutes	6.8 (0.5-19.4)	Mann-Whitney-U	4.7 (0.5-17.6)	8.2 (0.7-19.4)	464.0	0.007**	5.2 (0.8-19.4)	2.8 (0.8-12.0)	122.5	0.254	10.1 (1.1-15.9)	4.4 (0.8-14.4)	248.0	0.002**
SOREM count in MSLT, n	0.5 (0-5.0)	Mann-Whitney-U	2.0 (0-5.0)	0 (0-5.0)	1084.5	<0.001***	0.5 (0-4.0)	3.0 (0-5.0)	42.5	0.018*	0 (0-4.0)	2.0 (0-5.0)	62.0	0.002**
Cataplexy, yes, %	30.5	Chi-square	53.7a	7.7b	17.576	<0.001***	30.8a	75.0b	4.941	0.026*	0.0	54.2	11.527	0.001**
Sleep paralysis, yes, %	46.3	Chi-square	61.0a	30.8b	7.336	0.007**	46.2a	87.5b	4.242	0.039*	35.7	66.7	3.426	0.064
Hallucinations, yes, %	37.5	Chi-square	51.2a	23.1b	6.754	0.009**	50.0	75.0	1.551	0.213	28.6	62.5	4.071	0.044*

The values that were designated with different letter in each row were significantly different from each other in pairwise group comparison. Chi-square was used for categorical variables, Mann-Whitney-U was used for continous variables. Significant results was demonstrated in bold. p<0.05*, p<0.01**, p<0.001***,

HLA: Human leukocyte antigen, MSLT: Multiple sleep latency test, RBD: REM sleep behaviour disorder, RWA: REM sleep without atonia, SOREM: Sleep onset REM, WASO: Wakefullness after sleep onset

were found to be less associated with narcolepsy and its clinical or polysomnographical features, rather more related other-CDH and non-CDH groups. The autoimmune nature of NT1 was well documented in the literature[16] via (1) the hypocretinergic / orexinergic neural loss due to a predominantly T-cell mediated inflammatory infiltration, (2) consequently decreased hypocretin/orexin levels in cerebrospinal fluid, (3) significant temporal and causal association with certain pre-morbid infections or vaccinations,[17,18] especially documented during H1N1 pandemic and H1N1 vaccination, and (4) HLADQB1*0602 phenotype positivity up to 98% of NT1, including both idiopathic[19] and vaccine-triggered cases,[20] which is also an important data about the genetic predisposition of NT1.[21] Despite a large body of evidence for immune and genetic background of NT1, the similar pathogenetic mechanisms could not be shown in NT2 or IH so far. Although it is known that HLADQB1*0602 positivity can be detected up to 40-60% of patients with NT2 and also 5-30% of normal healthy population, some authors claim that it may be a clue for conversion to NT1 in initially diagnosed as NT2 or IH.[22] The unresolved problem is whether this must be regarded as a disease progression, that suggest a continuous pathological spectrum from NT2-IH to NT1, or just as an initial misdiagnosis due to the partial lack of characteristic symptoms of NT1, like cataplexy. The roots of this question extend to the absence of established immune or genetic mechanisms related to the hypersomnolence subtypes apart from NT1. A recent study performed by Gool et al.[23] investigated the potential immunological triggers for NT2 and IH in a large cohort, and it was revealed that infection and/or vaccination were reported before the development of NT2 and IH in 36/71 individuals (50.7%) and infections were mainly caused by Ebstein-Barr virus, followed by other respiratory infections. On the other hand, the well-defined infectious triggers of NT1, flu and influenza vaccination were uncommon in NT2 and IH.[23] Surprisingly, 80% of patients with NT2 in this cohort were HLA antigens DQB1*0602 positive.[23] When this evidence about the possible immunological triggers and genetic predisposition in NT2 and IH was taken into account with the data presented in this article about the shared HLA antigens phenotypes among non-NT1 hypersomnolence subtypes, revealing the need to extend this work in broader analyses of HLA antigens system and its interrelationship with the systemic immunological markers.

Study Limitations

This study has certain limitations. (1) The interpretation of the DQB1*03 subtype as a common marker of hypersomnolence with similar distribution among different types of diagnosis needs to be grounded by the healthy population carrier frequencies. (2) To manage the discrimination of different CDH categories from each other by HLA antigens typing, the study population must be larger enough to subcategorise each CDH defined in ICSD-3-TR. (3) More comprehensive implications of HLA antigens typing on the differential diagnosis of EDS/hypersomnolence require the analysis of each of the class I (A, B, C) and class II alleles of HLA antigens (DR, DQ, DP) in all study subjects, that was not possible within the scope of this study. (4) The lack of cerebrospinal fluid hypocretin measurement and the sub-analysis of HLADQB1*06 positive subjects for the presence/absence of DQB1*0602 was also a limitation for the diagnostic certainty and confirmation of NT1 cases.

Conclusion

By revealing the role of DQB1*06 in differentiating narcolepsy type 1 (NT1) from non-NT1, this study aligns with existing research and emphasizes its diagnostic significance. Moreover, DQB1*03 has been identified as a prominent common marker for hypersomnolence, while DQB1*02 is more frequently associated with non-narcolepsy CDH.

Ethics

Ethics Committee Approval: This study was conducted with a retrospective design in the sleep and disorders units of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine and Aydın Adnan Menderes University, Faculty of Medicine, after the approval of the Ethics Committee of the İstanbul University-Cerrahpaşa (approval number: 15.11.2023-837477, date: 15.11.2023).
Informed Consent: Informed consent had been obtained from all the study participants to get an allowance to investigate past medical records.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.A.S., B.Z., U.O.A., D.K., G.B.Ş., Concept: M.A.S., G.B.Ş., Design: M.A.S., G.B.Ş., Data Collection or Processing: M.A.S., B.Z., E.Y., G.B.Ş., Analysis or Interpretation: M.A.S., U.O.A., D.K., G.B.Ş., Literature Search: M.A.S., E.Y., Writing: M.A.S.
Conflict of Interest: Gülçin Benbir Şenel, MD, is the editor of the Journal of Turkish Sleep Medicine. She had no involvement in the peer-review process of this article and had no access to information regarding its peer review. The other authors have no conflicts of interest to disclose.
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