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Original Article

Thyroid autoimmunity in relation to HLA-DRB1 and HLA-DQB1 polymorphism in nonsegmental vitiligo: a cross-sectional-study

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Abstract: Objectives: Nonsegmental vitiligo (NSV) is frequently associated with thyroid autoimmunity (TAI), however, the immunopathogenic mechanisms of such association remain to be investigated. The aims of this work were to estimate the frequency of TAI and to describe the genetic polymorphism in the human leukocyte antigen (HLA)-DRB1 and -DQB1 loci in TAI susceptibility among patients with NSV. Patients and methods: In this cross-sectional study, screening for TAI was performed in 97 Moroccan patients with NSV by measuring antibodies against thyroid peroxidase (TPOAb) and thyroglobulin (TGAb). HLA-DRB1 and -DQB1 were determined with single specific primer-polymerase chain reaction (PCR-SSP) typing methods. Results: TAI was diagnosed in 20 patients with NSV (20.6%). The phenotypic frequency of DQB1*05 (OR = 5.04; P = 0.006; pc = 0.036) was significantly higher in NSV patients with TAI. Genotype DQB1*05/DQB1*06 (OR = 25.33; P = 0.001; pc = 0.003) confer susceptibility to TAI in NSV patients. NSV patients with TAI and early onset vitiligo have an extremely high phenotype frequency of DQB1*05 allele (OR = 14.67; P = 0.001; pc = 0.048) and DQB1*05/DQB1*06 genotype (OR = 26.55; P = 0.01; pc = 0.03). TAI in patients with NSV was (6.2%) associated with onset of clinical thyroid disease based on TSH and free T4. Conclusion: Our findings suggest that HLA-DQ polymorphisms influence TAI risk in subjects with NSV, although HLA does not completely explain the co-occurrence of these two diseases.

Keywords: Nonsegmental vitiligo, thyroid autoimmunity, HLA, Moroccan population

Introduction

Co-occurrence of thyroid autoimmunity (TAI) and vitiligo/non-segmental vitiligo (NSV) in diverse ethnic populations is well established [1, 2]. Vitiligo develops through a complex interaction of environmental and immunogenetic factors and is characterized by inflammatory and T cell-mediated autoimmune reaction against unknown autoantigen of melanocytes [3-6]. Antibodies (Abs) against thyroid peroxidase (TPOAbs) and thyroglobulin (TGAbs) play a crucial role in the induction of thyroid disease pathogenesis [7]. These Abs are produced by plasma cells concurrently with helper CD4+ T cell infiltration in the thyroid tissue [8], with TPOAbs considered a key immunological marker of TAI [9]. The frequency of these Abs has been observed to be higher in vitiligo subjects, particularly those with NSV, in comparison to the general population [10] and varies widely [11]. The events that lead to the generation of these Abs in NSV patients are poorly understood and likely result from a complex interaction of immunogenetic [12-14] and environmental factors (e.g., chronic inflammatory milieu, heavy metals, pollutants, ionizing radiation, and other chemical substances) [15, 16] that allow breakdown of tolerance to both modified thyroxine and melanin proteins, leading to the frequently reported association of TAI and NSV [17, 18]. The major immunogenetic risk factor for TAI has been mapped to the human leukocyte antigen class II (HLA-II) region, especially the HLA-DQB1* loci [19-21]. HLA-DQ genotype has been associated with either TPOAbs, TGAbs or both in subjects with type 1 diabetes [22, 23]. HLA-DQA1*0302, -DQA1*0601, -DQB1*0303, -DQB1*0503, and -DQB1*0201 alleles have been associated with vitiligo in

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diverse ethnic populations [24-26], although their relationship with TAI in vitiligo remains unknown and requires further research. We hypothesized that association of TAI with NSV could be determined by HLA-DR and -DQ polymorphisms. Therefore, in this work, we investigated in Moroccan subjects with NSV: (1) the frequency of TAI; and (2) the possible association between TAI, with HLA-DRB1 and -DQB1 loci.

Patients and methods

Research study design was approved by Mohammed V University Ethics Committee, Rabat, Morocco. All blood samples and clinical information were obtained after informed consent was signed.

Patients

In the present cross-sectional study, we recruited 97 unrelated Vitiligo/NSV subjects presenting consecutively to the Department of Dermatology at Rabat Ibn Sina University Hospital from January 2009 to December 2018. The diagnosis of NSV was based on clinical evaluation, including daylight and Wood's lamp examination. Patients with other forms of vitiligo (mixed, segmental, focal, mucosal, and not classifiable) were excluded from the study. The diagnosis of TAI relies on the presence of significant levels of serum TPOAbs and/or TGAbs or evidence of autoimmune thyroiditis. All of the patients were of Moroccan origin.

HLA typing

HLA-DRB1 and -DQB1 loci were determined with low-resolution polymerase chain reaction-sequence-specific primer (PCR-SSP) according to Micro SSP deoxyribonucleic acid (DNA) Typing Trays protocol.

Autoantibodies to TPO and TG

The serum samples for TPO/TG Abs detection were collected in the first visit of our clinics in all vitiligo subjects. The IgG TPOAbs and TGAbs were analyzed by Luminex® Technology. A concentration >120 UI/ml was considered positive.

Serum thyroid-stimulating hormones and free thyroid hormone T4

Analysis of thyroid-stimulating hormones (TSH) and free thyroxine (FT4) was performed by chemiluminescence (Abbott Park, Middletown, USA). Hyperthyroid disease was diagnosed when TSH<0.01 mU/l and FT4>22 pmol/l and for hypothyroid disease when TSH>8 mU/l and FT4<12 pmol/l.

Statistical methods

Statistical analyses were performed using SPSS software (version 13.0; SPSS, Chicago, IL, USA). The quantitative variables were expressed as median (interquartile range) with using Mann-Whitney U nonparametric test for comparing variables between study groups. Differences in proportions between groups were tested using the Chi-square test or Fisher's two-tailed exact probability test as appropriate (when one or more of the expected numbers in the 2×2 table is less than five). Odds ratios (OR) and their 95% confidence intervals (CI) were also calculated. When some of the analyzed frequencies were zero, OR was adjusted by Haldane's modification. All *P* values for HLA-DRB1* and -DQB1* alleles associations were corrected (pc) for multiple testing using Bonferroni's method; namely, pc was corrected by multiplying the number of observed comparisons. P<0.05 was considered significant.

Results

Patients' features

A total of 97 subjects with NSV were included (**Table 1**). There were 62 (63.9%) women and 35 (36.1%) men (sex ratio M/F: 0.87). The median age of subjects was 42 (29-52) years. At the time of diagnosis, a total of 20.6% (20/97) of the NSV patients were positive for either TPOAb (15.5%; 15/97), TGAb (14.4%; 14/97) or both (9.3%; 9/97). The documented clinical and biological signs suggest that of the patients studied, there may be seven with hypothyroid disease and two with hyperthyroid disease (9.3% of the entire study group).

TAI in relation to clinical features of NSV

A comparison of clinical and biological characteristics between NSV subjects with and without TAI is presented in **Table 2**. No significant association for TAI was found for familial vitiligo, early-onset vitiligo, age at presentation, and sex distribution. Patients with TAI had a 12.5-fold increased odds of hypothyroidism at diag-

Table 1. Clinical and biological parameters from 97 patients with NSV

Clinical and biological parameters	
Sex	
Female n (%)	62 (63.9)
Male n (%)	35 (36.1)
Age at consultation	42 (29-52) years
Disease onset (median age)	23 (9.5-39.5) years
Family history of vitiligo n (%)	37 (38.1)
Elevated Autoantibodies rate n (%)	
TPO Ab	15 (15.5)
Tg Ab	14 (14.4)
TPO, Tg or both	20 (20.6)
Clinical thyroid disease n (%)	
Hypothyroid disease[a]	7 (7.2)
Hyperthyroid disease[b]	2 (2.1)

n: number of patients; TPO Ab: anti-thyroid peroxidase antibodies; TG Ab: anti-thyroglobulin antibodies; [a]TSH>8 mU/l, FT4<10 pmol/l; [b]TSH<0.01 mU/l, FT4>22 pmol/l.

nosis of NSV compared with NSV subjects without TAI (25% vs 2.6 %; P = 0.004). The seven patients with hypothyroid disease also had increased levels of anti-TPO Abs (262-636 UI/ml) and -TG Abs (231-407 UI/ml) (data not shown).

TAI in association with HLA

The phenotypic frequencies of HLA-DRB1 and -DQB1 alleles and selected genotypes in patients with NSV with and without TAI are shown in **Table 3**. The DQB1*05 allele conferred significant risk of TAI in patients with NSV. DQB1*05 was carried by 8/20 (40%) of NSV with TAI compared to 9/77 (11.7%) of NSV without TAI, giving an OR of 5.04 (95% CI 1.62-15.64; P = 0.006; pc = 0.036). Three other HLA alleles showed suggestive evidence of frequency differences between subgroups with and without TAI based on nominal significance levels. DRB1*16 (P = 0.041; pc = 0.574) and DQB1*04 (P = 0.029; pc = 0.174) were significantly increased, and DRB1*07 (P = 0.039; pc = 0.546) was significantly decreased in patients with TAI. Among genotypes, a positive association was found for HLA-DQB1*05/DQB1*06 genotype and TAI (OR = 25.33; P = 0.001; pc = 0.003).

To identify whether the TAI risk level was influenced by age at onset of vitiligo/NSV, we divided the study group into two categories: those with onset at 20 years or younger were defined as clinical early-onset NSV, and those with onset older than 20 years were categorized as clinical late-onset NSV. As shown in **Table 4**, DQB1*05 allele (OR = 14.67; P = 0.008; pc = 0.048) and DQB1*05/DQB1*06 genotype (OR = 26.55; P = 0.01; pc = 0.03) conferred significant risk against TAI in the early-onset subgroup, whereas no differences in HLA in TAI were found in the late-onset subgroup.

Discussion

We have found that 20.6% of NSV patients were positive for either TPOAb (15.5%), TGAb (14.4%) or both. Our results are in agreement with previous findings in diverse ethnic populations using similar methods and diagnosis criteria [27-30]. Furthermore, only a few NSV patients with TAI (5 patients) are diagnosed with overt or subclinical hypothyroidism. It has been estimated that 59% of NSV patients with TAI have been diagnosed with hypothyroidism or subclinical thyroid disease [31]. Indeed, the risk of subjects with vitiligo developing future overt hypothyroidism is correlated with TPOAb titers [32], suggesting that subjects should be regularly screened for high TPOAb titers and hypoechogenic ultrasonography patterns.

While the association between patients without anti-TPO Abs and HLA-DRB1*07-DQB1*02 haplotype has been described previously [33], it was a novel finding that HLA-DQB1*05 allele confers susceptibility to TAI in patients with NSV. Our study therefore indicates that primarily DQB1*05/DQB1*06 genotype predisposes patients with NSV against developing TAI. An association between TAI and DQB1*05 [34], DRB1*04-DQB1*03:01 [35], DQw4 [36], DQB1*02:02, *06:03, *06:09, *03:02, and *03:03 [21] has been reported. Positive associations were also reported for HLA-DQA1*03:02, -DQB1*03:03, and -DQB1*05:03 alleles with vitiligo in the Chinese population [24]. Another potential link to TAI was also observed with variations in amino acids within the peptide-binding pockets of DQB1* alleles [21]. However, the positive effect of DRB1*07 observed in NSV patients [33] is not observed in a subgroup with TAI. This suggests that DRB1*07 does not act as a susceptible HLA-allele for TAI, namely, does not contribute to the

Table 2. Clinical features in NSV patients with and without TAI

	NSV without TAI n = 77 (%)	NSV with TAI n = 20 (%)	*p*
Sex			
Female	48 (62.3)	14 (70)	0.525
Male	29 (37.7)	6 (30)	
Mean age	36.27 ± 16.44	42.55 ± 13.71	0.089
Disease onset (mean age)	24.69 ± 17.57	26.62 ± 16.07	0.642
Age at disease onset <21 yrs	36 (46.8)	7 (35)	0.346
Age at disease onset >20 yrs	41 (53.2)	13 (65)	
Family history of vitiligo	31 (40.3)	6 (30)	0.4
Clinical thyroid disease			
Hypothyroid disease[a]	2 (2.6)	5 (25)	0.004*
Hyperthyroid disease[b]	1 (1.3)	1 (5)	0.372

NSV: Nonsegmental vitiligo; n: number of patients; [a]TSH>8 mU/l, fT4<10 pmol/l; [b]TSH<0.01 mU/l, fT4>22 pmol/l; *OR = 12.5, 95% CI 2.21-70.58.

Table 3. Phenotype frequency of DRB1 and DQB1 alleles and selected genotypes in NSV with TAI vs without TAI

	NSV without TAI (n = 77)		NSV with TAI (n = 20)		NSV with TAI vs without TAI			
	n	%	n	%	*P*	*pc*	OR	CI
HLA-DRB1*								
DRB1*01	6	7.8	3	15	0.386*	>1		
DRB1*03	15	19.5	3	15	0.758*	>1		
DRB1*04	22	28.6	5	25	0.751	>1		
DRB1*07	35	45.5	4	20	0.039	0.546	0.3	0.092-0.980
DRB1*08	5	6.5	2	10	0.631*	>1		
DRB1*09	1	1.3	2	10	0.107*	>1		
DRB1*10	3	3.9	0	0	1*	>1		
DRB1*11	14	18.2	1	5	0.185*	>1		
DRB1*12	2	2.6	0	0	1*	>1		
DRB1*13	23	29.9	8	40	0.387	>1		
DRB1*14	1	1.3	1	5	0.372*	>1		
DRB1*15	16	20.8	4	20	1*	>1		
DRB1*16	0	0	2	10	0.041*	0.574	25.33**	2.76-232.62
HLA-DQB1* allèles								
DQB1*02	45	58.4	8	40	0.14	0.84		
DQB1*03	44	57.1	8	40	0.171	>1		
DQB1*04	5	6.5	5	25	0.029*	0.174	4.80	1.23-18.68
DQB1*05	9	11.7	8	40	0.006*	0.036	5.04	1.62-15.64
DQB1*06	32	41.6	9	45	0.781	>1		
HLA-DQB1* genotypes								
DQB1*05/05; 05/X[a]	9	11.7	8	40	0.006*	0.018	5.04	1.62-15.64
DQB1*05/06	1	1.3	5	25	0.001*	0.003	25.33	2.76-232.62
DQB1*05/X[b]	8	10.5	2	14.3	0.651			

OR = Odds Ratio; CI = confidence interval; p = stand *p*-value; pc = corrected *p*-value. *Fisher's exact *p*-value (two-tailed). X[a] is any allele; X[b] is not DQB1*06 or DQB1*04.

Table 4. Phenotype frequency of HLA-DQB1 alleles and selected genotypes in patients with early onset NSV versus late onset NSV

HLA-DQ	Early onset NSV (Age <21)				OR	95% CI	Late-onset NSV (Age >20)			
	TAI positive (n = 7)	TAI negative (n = 36)	*p*	*pc*			TAI positive (n = 13)	TAI negative (n = 41)	*p*	*pc*
DQB1*alleles										
DQB1*02	2 (28.6)	23 (63.9)	0.11*	0.66			6 (46.2)	22 (53.7)	0.367	>1
DQB1*03	2 (28.6)	19 (52.8)	0.412*	>1			6 (46.2)	25 (61)	0.346	>1
DQB1*04	2 (28.6)	3 (8.3)	0.18*	>1			3 (23.1)	2 (4.9)	0.084*	0.504
DQB1*05	4 (57.1)	3 (8.3)	0.008*	0.048	14.67	2.19-98.78	4 (30.8)	6 (14.6)	0.230*	>1
DQB1*06	4 (57.1)	16 (44.4)	0.687*	>1			5 (38.5)	16 (39)	0.971	>1
DQB1*genotypes										
DQB1*05/05; 05/X[a]	4 (57.1)	3 (8.3)	0.008*	0.024	14.67	2.19-98.78	4 (30.8)	6 (14.6)	0.230	0.69
DQB1*05/06	3 (42.9)	1 (2.8)	0.01*	0.03	26.25	2.18-3016.09	2 (15.4)	0	0.055*	0.165
DQB1*05/X[b]	0	2 (5.7)	1*	>1			2 (18.2)	6 (14.6)	1*	>1

OR = Odds Ratio; CI = confidence interval; p = stand *p*-value; pc = corrected *p*-value. *Fisher's exact *p*-value (two-tailed). X[a] is any allele; X[b] is not DQB1*06 or DQB1*04.

increase of serum levels of anti-TG and -TPO-autoantibodies. These findings, along with the documented association between HLA-DQ and TAI in diverse ethnic populations, highlight the likely importance of DQB1* alleles for the risk of TAI in NSV.

The high-risk genotype for TAI, DQB1*05/DQB1*06, predominates in NSV patients with early-onset, which contributes substantially to the heritability difference between the early-onset and late-onset subgroups. Differences in HLA-DQ haplotype frequencies according to the age at onset of vitiligo have been found in other studies [37]. Thus, it is speculated that aberrant antigen presentation by HLA-DQ molecules could sensitize autoreactive CD4+ T lymphocytes or fail to select FOXP3+ regulatory T lymphocytes [38], and thus may both increase overall TAI risk and accelerate vitiligo onset. This process is likely initiated by environmental insult [15, 16], though it is unknown what triggers may specifically influence the early-onset group, which appears to be particularly relevant to NSV associated with the DQB1*05/DQB1*06 genotype.

Consistent with findings in other studies, we did not observe a significant relationship between TAI and familial history of vitiligo, age at onset of vitiligo, age at presentation, and sex distribution [31]. However, Gey et al. found age at onset of vitiligo/NSV (<18 years/≥18 years) and female sex were associated with TAI-NSV [31]. The described difference in clinical features of NSV can be attributed to the low sample size of the study group and to the lack of an internationally accepted cut-off point of age at onset of vitiligo [39-41].

There are a few limitations to our study, one of which is that the results were only based on lower resolution (1st and 2nd field) HLA typing of HLA-DRB1 and -DQB1 loci upon the sampling at onset of vitiligo. Confirmation of these findings will require further studies in larger sample sizes, including analysis of allelic and haplotype diversity of HLA-DQB1 and -DQA1 loci at high-resolution (4th field level) HLA typing.

In conclusion, individuals with NSV were more likely to develop TAI. HLA-DQB1*05 including DQB1*05/DQB1*06 may confer susceptibility to TAI and early onset vitiligo. These findings may have implications for the clinical management of NSV subjects. Further studies are, therefore, needed to validate our findings in other, and possibly larger, clinical cohorts that are directly genotyped for HLA-DQB1 and -DQA1 loci.

Disclosure of conflict of interest

None.

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