Differences in genetic predisposition to Graves' disease (GD) and Graves' orbitopathy (GO) between young and elderly patients.

Beata Jurecka-Lubieniecka[1], Aleksandra Krol[1], Sylwia Szpak-Ulczok[1], Tomasz Bednarczuk[2], Rafal Ploski[3], Dorota Kula[1], Andrzej Tukiendorf[4], Zofia Kolosza[4], Barbara Jarzab[1]

[1]Department of Nuclear Medicine and Endocrine Oncology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland;
[2]Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Warsaw, Poland;
[3]Department of Medical Genetics, Forensic Medicine, Medical University of Warsaw, Warsaw, Poland
[4]Department of Epidemiology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland;

Introduction

Graves' disease is a complex disorder. Genetic predisposition modified by environmental factors is responsible for the pathogenesis of GD. Young patients are susceptible to environmental factors for a shorter time than older patients, thus the impact of genetic factors may be higher than environmental factors in patients with young age of GD diagnosis. Differences in the disease phenotype between younger and older patients may suggest a different genetic predisposition to the GD. The association between genetic markers and the age at the diagnosis was reported in type I diabetes, rheumatoid arthritis and multiple sclerosis.

Orbitopathy (GO) and GD hyperthyroidism have the common autoantigen TSHR which plays a key role in triggering the onset of the disease. Taking into account the diverse nature of the GO phenotype, especially in young patients and lack of the relation of time of the GO with development of hyperthyroidism, the pathogenesis of GD and GO may correlate with different genetic backgrounds. Current studies suggest a correlation between polymorphism in cytokines involved in orbit inflammation and GO, but not GD. It has been confirmed that GO risk increases with age and is considerably higher in smokers.

The aim of the study was to asses genetic predisposition to GD and GO in young patients (age of diagnosis ≤ 30 years of age) in which the time of environmental effects was shorter than in older patients.

Methods

735 GD patients and 1216 healthy controls from Poland were included in the study. 338 of the patients had orbitopathy NOSPECS ≥ 2. Association analyses were performed between genetic variants in genes encoding proteins involved in immunoresponse (***HLADRB1, TNF, CTLA4, CD40, NFKb, PTPN22, IL4 and IL10***), ***RTSH*** and the age of diagnosis of GD and GO. Patients were stratified by the age of diagnosis of GD and GO.

Results

Our analysis demonstrated an association between HLA DRB01*03 and the age of GD diagnosis. Patients with age ≤30 years at GD diagnosis had higher frequency of the HLA DRB1*03 allele. The genotype containing at least one DRB1*03 allele occurred almost twice as often in younger patients (Tab. 1). Young carriers of the DR3 polymorphism were more common then the older ones both in familial and sporadic GD. This results suggest the existence of different genetic conditions for the development of GD in young people.

No association was observed between DRB1*03 allele and the duration of pharmacotherapy, GD relapse rate, number of radioiodine treatment courses, thyroid receptor (TR) Ab level and gender.

Tab. 1. HLA DRB1*03 genotypes in patients with GD stratified by the age at GD diagnosis.

SNP	Genotype	GD ≤30 n (%)	GD >30 n (%)	OR (95% CI); p
HLA-DRB1*03	DR3-/-	42 (42)	196 (61)	Reference
	DR3-/+	56 (55)	118 (37)	2.21 (1.36-3.61); p< 0.001
	DR3+/+	3 (3)	7 (2)	2.00 (0.31-9.18); ns
	DR3-/+ and +/+ *	59 (58)	125 (39)	2.20 (1.36-3.57); p<0.001

* carriers of minor alleles

We found a significant association between orbitopathy and HLA DRB1*03 and TSHR gene rs179247 polymorphisms.

We observed a higher frequency of the HLA DRB1*03 allele in young patients with GO (p<0.01)(Tab. 2).

Tab. 2. Distribution of HLA DRB1*03 polymorphism in GD patients stratified by the age of diagnosis of GO.

SNP	Genotype	NOSPECs	GD≤30 n(%)	GD>30 n(%)	p
HLA DRB1*03	DR32/2	2+	15 (35.7)	112(63.6)	0.001
	DR32/+ and +/+		27 (64.3)	64 (36.4)	
	DR32/2	0 - 1	26 (44.8)	84 (57.9)	Ns 0.062
	DR32/+ and +/+ *		32 (55.2)	61 (42.1)	

* carriers of minor alleles

In younger patients without orbitopathy the A allele of TRSH gene rs179247 occurred significantly more often in comparison with those with GO (p<0.013). In younger patients group there was a statistically significant difference in genotype distribution (p<0.038).The presence of an AA homozygous locus was associated with a significant reduction in the risk of GO incidence as compared to patients with AG or GG genotypes (p<0.019)(Tab. 3).

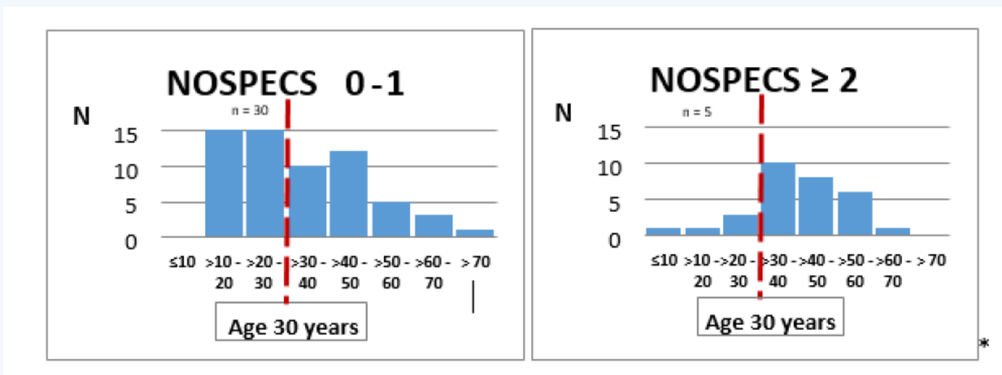
Tab. 3. Distribution of rs179247 TSHR alleles and genotypes in GD patients with and without GO

gen/SNP	allele/ genotype	all patients			patients ≤ 30 years at diagnosis		
		GD without GO	GD with GO	OR (95%CI) p	GD without GO	GD with GO	OR (95%CI) p
TSHR rs179247		N = 316 (100%)	N = 283 (100%)		N = 104 (100%)	N = 73 (100%)	
	G	302 (47.8%)	280 (49.5%)	0.93(0.74-1.18)p<0.56	87 (41.8%)	81 (55.5%)	0.58 (0.37-0.90) p<0.013
	A	330 (52.2%)	286 (50.5%)		121 (58.2%)	65 (44.5%)	
	GG	77 (24.4%)	77 (27.2%)	0.71	20 (19.2%)	22 (30.1%)	0.038
	AG	148 (46.8%)	126 (44.5%)		47 (45.2%)	37 (50.7%)	
	AA	91 (28.8%)	80 (28.3%)		37 (35.6%)	14 (19.2%)	
	AA vs GG+AG			0.97 (0.68-1.39) p<0.88			0.43 (0.20-0.91) p<0.019

In our study the allele A carriers were dominant in the group of patients with orbitopathy (N=145 vs N=90), especially in young patients group (N=64 vs N=28). Orbitopathy was not present in 86% of young AA homozygote carriers (N=30 vs N=5)(Fig. 1).

These findings showed the association between the presence of the allele A and lesser risk of GO in young GD patients.

Fig. 1. Incidence of GO in patients with age at GD diagnosis ≤30 years and with the AA genotype TSHR rs 179247.



In the group of all patients or only older patients (age at diagnosis >30 years) the frequency of alleles present and genotype distributions of polymorphisms HLA DRB1 and TSHR rs179247 did not differ in patients with or without GO.

Conclusions

1. Polymorphism of HLA DRB1*03 is associated with an early age at diagnosis of GD.
2. Carriers of the HLA DRB1*03 allele are significantly more common in young patients with GO.
3. The allele A of the rs179247 polymorphism in the TSHR gene is associated with a lower risk of GO in young patients with GD.

Bibliography

1. Jurecka-Lubieniecka B., Bednarczuk T., Ploski R., Krajewska J., Kula D., Kowalska M., Tukiendorf A., Kolosza Z., Jarzab B. Differences in gene-gene interactions in Graves' disease patients stratified by age of onset. *PLoS One 2016*, 4,11(3), e0150307.
2. Jurecka-Lubieniecka B., Ploski R., Kula D., Szymanski K., Bednarczuk T., Ambroziak U., Hasse-Lazar K., Hyla-Klekot L., Tukiendorf A., Kolosza Z., Jarzab B. Association between Polymorphisms in the TSHR Gene and Graves' Orbitopathy. *PLoS One*, 2014, 9, 7, e102653.
3. Jurecka-Lubieniecka B., Ploski R., Kula D., Krol A., Bednarczuk T., Kolosza Z., Tukiendorf A., Szpak-Ulczok S., Stanjek-Cichoracka A., Polanska J., Jarzab B. Association between age at diagnosis of Graves' disease and variants in genes involved in immune response. *PLoS One*, 2013, 8, 3, e59349.
4. Płoski R., Brand O. J., Jurecka-Lubieniecka B., Franaszczyk M., Kula D., Krajewski P., Karamat M. A., Simmonds M. J., Franklyn J. A., Gough S. C., Jarząb B., Bednarczuk T. Thyroid stimulating hormone receptor (TSHR) intron 1 variants are major risk factors for Graves' disease in three European Caucasian cohorts. *PLoS One*, 2010, 5, 11, e15512.