MHC class II antigens in alopecia areata

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ABSTRACT

Introduction. In accordance with assumption of a possible autoimmune nature of alopecia areata, the purpose of this study was to investigate associations between alopecia areata and MHC class II antigens (DR and DQ loci).

Materials and methods. The study was performed on 23 patients with alopecia areata, classified in two groups, on the basis of severity of clinical picture: 13 alopecia totalis/universalis and 10 unilocular/multilocular alopecia areata patients.

MHC class II antigens were determined by double staining immunofluorescence. Seventeen antigens were determined for DR locus, and 9 antigens for DQ locus. For all antigens phenotypic frequency and relative risk were calculated. The Control group consisted of 114 healthy tissue and organ donors. Chi square test for small samples was used in statistical analysis.

Results. Significantly higher frequencies of DQ2, and smaller of DR1 antigens were detected in the whole group. In alopecia totalis/universalis subgroup a significantly higher frequency of the DQ2 and a smaller one of DQ3(9) antigens were observed. In the unilocular/multilocular alopecia areata subgroup only a significant decrease of the DQ3(9) frequency was found.

Conclusion. It can be assumed that an increased frequency of DQ2 increases the risk of severe forms of alopecia areata while the absence of DQ3(9) may have some protective role. Further studies on a larger number of patients are however necessary.

KEY WORDS

Alopecia areata, HLA Class II antigens, DR, DQ

Introduction

Alopecia areata (AA) is a non-cicatricial alopecia of unknown etiology. Findings of CD4+, CD8+ lymphocytes and CD1+ cells in perivascular, peribulbar and intrafollicular infiltrate, an up-regulated expression of MHC class I molecules in hair follicles, hair follicle specific auto-antibodies, possible associations with immune disorders as well as a beneficial effect of immune-modulating agents support the assumption that AA is an autoimmune disorder. In accordance with such a supposition we decided to investigate the associations between AA and MHC class II antigens, the DR and DQ loci in patients from Vojvodina.

Table 1. DQ locus antigen frequency in total group of alopecia areata patients

DQ antigens	AA	FFAA	K	FFK	RR	X^2
DQ1	15	0,652	91	0,631	1,09	0,0021
DQ1 (5)	0	0	9	0,0625	0	2,99
DQ1 (6)	0	0	4	0,027	0	0,12
DQ2	**10**	**0,434**	**18**	**0,125**	**5,45**	**11,51****
DQ3	6	0,260	51	0,354	0,64	1,24
DQ3 (7)	3	0,130	14	0,097	1,39	0,01
DQ3 (8)	0	0	2	0,013	0	2,56
DQ3 (9)	0	0	1	0,006	0	3,45
DQ4	0	0	8	0,055	0	2,84
DQX	12	0,520	88	0,611	0,69	1,08

** - statistical significance $p< 0,0001$
AA - alopecia areata patients group
FFAA - phenotypic frequency in patients with alopecia areata
K- control group of healthy organ and blood donors
FFK - phenotypic frequency in control group
RR - relative risk

Materials and methods

Twenty-three patients with AA were separated into two groups according to the severity of clinical symptoms: 13 alopecia totalis/universalis (AT/U) and 10 unilocular/multilocular (AU/M) AA patients. In 12 of the patients alopecia lasted more than one year, and in 11 less than that. Familial occurrence of AA was not noted in any of our patients, but in 3 patients other presumably autoimmune disorders were identified: vitiligo, primary hypothyreoidism and psoriasis vulgaris, and insulin dependent diabetes mellitus.

MHC class II antigens were determined by two-colored immunofluorescent method, using immunomagnetic technique. 17 antigens were determined for DR locus, and 9 antigens for DQ locus. Phenotypic frequency (PF) and relative risk (RR) were calculated for all antigens. A control group (K) consisted of 114 healthy, tissue and organ donors. Chi square test (X^2) for small samples was used for the statistical analysis ($p<0.05$ statistical significance).

Results

In the whole group of AA patients a significantly higher frequency of DQ2 (RR=5.45; X^2= 11.51), and smaller frequency of DR1 antigens (RR= 0.206; X^2= 3.85) were detected. Table 1. In AT/U subgroup, significant higher frequency of DQ2 antigen (RR= 16.33; X^2= 18.70) was confirmed, together with a lower frequency of DQ3(9) antigen (RR= 0; X^2= 5.29). Table 2. In AU/M subgroup only a significantly decreased frequency of DQ3(9) antigen (RR= 0; X^2= 4.50) was found. Table 3.

Discussion

The HLA system has an important role in immune response and in autoimmunity regulation (1). By presenting self and non-self antigens to the immune system, it controls the production of T lymphocytes by determining their selection processes in the thymus. Genes of MHC class I, code for polymorphous membrane glyco-proteins, presenting self and non-self proteins to CD8+ lymphocytes, while class II MHC antigens as membrane molecules, present self and non-self antigens to CD4+ T cells. Taking into consideration the facts that AA is genetically determined disease of autoimmune nature, HLA typification can contribute to the hereditary aspect of this disorder (2, 3).

In the past investigations of a possible association between HLA and AA were directed towards HLA class I antigens (A and B loci). The results obtained were controversial. Kiant et al. found a significantly higher frequency of HLA B12 antigen, while Hachman-Zadeh observed an increased frequency of the HLA B18 antigen (4,5). Kuntz et al. did not confirm a statistically significant correlation between HLA class I antigens and AA (6). Similar results were obtained by Zlotogorski, who proved that even familial cases of AA were not associated with any of HLA antigens (7). Considering these and similar reports, it can be concluded that no consensus has been reached, concerning a possible

Table 2. DQ locus antigen frequency in alopecia totalis/ universalis group

DQ antigens	AT/U	FFAT/U	K	FFK	RR	X^2
DQ1	5	0,5	91	0,631	0,5824	1,37
DQ1 (5)	0	0	9	0,0625	0	2,06
DQ1 (6)	0	0	4	0,027	0	2,44
DQ2	**7**	**0,7**	**18**	**0,125**	**16,33**	**18,70****
DQ3	3	0,3	51	0,354	0,78	0,48
DQ3 (7)	1	0,1	14	0,097	1,031	0,27
DQ3 (8)	0	0	2	0,013	0	3,31
DQ3 (9)	**0**	**0**	**1**	**0,006**	**0**	**5,29***
DQ4	0	0	8	0,055	0	2,26
DQX	4	0,4	88	0,611	0,424	2,72

* - statistical significance $p< 0,05$
** - statistical significance $p< 0,0001$
AT/U - alopecia totalis/universalis
FFAT/U - phenotypic frequency in patients with alopecia totalis/universalis
K- control group of healthy organ and blood donors
FFK - phenotypic frequency in control group
RR - relative risk

correlation between AA and MHC class I system.

Studies on HLA class II antigens in AA are more consistent, especially for HLA DR4, DR5 and DQ3 antigens. Colombe et al. have confirmed a higher frequency of DQ3 (DQ7, DQ8), DR5 (DR11), and DR4 antigens (8). According to their research, AT/U group shows a significant association with the DQ3- subtype DQ7, and DR5 (DR11), which is not the case in patients with a less severe form of the disease, or in alopecia lasting less than 6 months. Such results favor the connection of alopecia totalis to DQ3 (DQ7) and DR11 antigens. This is in accordance with Welsh's statement about DQ3 antigen being a major marker of AA (9). According to Colombe et al., specific aminoacid sequence in the epithope common to all DQ3 antigens, (through molecular mimicry) may be responsible for AA. Further epithopes, such as DQ7 and DR11 exert influence on progression of the disease (8). Zhang's investigation on 55 Caucasian patients confirmed an association between AA and DR4, but not with DR5 or DQ antigens (10).

Table 3. DQ locus antigen frequency in alopecia unilocularis/ multilocularis group

DQ antigens	AU/M	FFU/M	K	FFK	RR	X^2
DQ1	10	0,769	91	0,631	1,941	0,17
DQ1 (5)	0	0	9	0,0625	0	2,41
DQ1 (6)	0	0	4	0,027	0	2,33
DQ2	3	0,23	18	0,125	2,1	0,42
DQ3	3	0,23	51	0,354	0,547	1,44
DQ3 (7)	2	0,153	14	0,097	1,688	0,03
DQ3 (8)	0	0	2	0,013	0	2,95
DQ3 (9)	**0**	**0**	**1**	**0,006**	**0**	**4,50***
DQ4	0	0	8	0,055	0	2,34
DQX	8	0,615	88	0,611	1,2727	0,07

* - statistical significance $p< 0.05$
AU/M - alopecia unilocularis/multilocularis
FFU/M - phenotypic frequency in patients with alopecia unilocularis/multilocularis
K- control group of healthy organ and blood donors
FFK - phenotypic frequency in control group
RR - relative risk

Our results for the whole group of AA patients support the role of the DQ2 antigen, which was also confirmed in AT/U patients. An increased frequency of this antigen was not confirmed in patients with less severe forms of the disease. A significantly decreased frequency of DQ1 was observed in the whole group of AA patients, and a decreased frequency of DQ3(9) in both AT/U and AU/M groups.

Conclusion

It can be assumed that an increased frequency of DQ2 increases the risk of severe forms of AA, while the absence of DQ3 (9) may have a protective role.

Further studies on a larger number of patients are however necessary.

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