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Distribution of HLA allele frequencies in patients with cystic echinococcosis in Latvia

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Распространение частоты HLA аллелей у пациентов с кистозным эхинококкозом в Латвии

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Summary

The incidence of echinococcosis in European countries varies from 0.1 to 10 cases per 100,000 residents and Latvia has relatively high number of cases. The development of cystic echinococcosis is associated with the individual factors of the host organism, as well as immunological reactions and HLA DRB1 is the most polymorphic of the HLA class II genes and therefore it can be used for individual identification.

We can conclude that in the case of cystic echinococcosis a more severe course of a disease can be anticipated in the presence of HLA DRB1 alleles *17:01 and *04:01, DQB1 *03:02, DQA1*04:01. As well in the event of cystic echinococcosis HLA DRB1 alleles *01:01 and *15:01, DQA1 *01:01 can be considered as protective.

Immunogenetic data could prove significant for therapy planning in accordance with the individual characteristics of a patient, because no data on the optimal duration of therapy and whether the therapy can be terminated without facilitating the relapse of the infection are not currently available.

Резюме

Частота эхинококкоза в европейских странах колеблется от 0,1 до 10 случаев на 100000 жителей, а в Латвии фиксируется относительно большое число случаев заболевания. Развитие кистозного эхинококкоза связано с отдельными факторами организма-хозяина, а также с иммунологическими реакциями, и HLA DRB1 является наиболее полиморфным для генов класса HLA II и поэтому его можно использовать для индивидуальной идентификации.

Мы можем заключить, что в случае кистозного эхинококкоза может наблюдаться более серьезное течение заболевания именно в присутствии аллелей HLA DRB1 * 17: 01 и * 04: 01, DQB1 * 03: 02, DQA1 * 04: 01. Кроме того, в случае кистозного эхинококкоза, аллели HLA DRB1 * 01: 01 и * 15: 01, DQA1 * 01: 01 можно причислить к протективным.

Иммуногенетические данные могут оказаться значимыми для планирования терапии в соответствии с индивидуальными характеристиками пациента, поскольку данные об оптимальной длительности терапии и о том, можно ли прекратить терапию без риска развития рецидива инфекции, в настоящее время недоступны.

Introduction

The incidence of echinococcosis in European countries varies from 0.1 to 10 cases per 100,000 residents [1,2,3]. The number of cases of echinococcosis diagnosed for the first time is rather high in Latvia as well, despite comparatively low population number. The location of Latvia next to endemic regions for this zoonotic disease, for instance, Russia, Belarus, Poland is also an important factor; however, no targeted studies on risk factors.

The development of cystic echinococcosis is associated with the individual factors of the host organism, as well as immunological reactions. It is known that susceptibility in humans varies; consequently, there are more susceptible individuals and non-susceptible or resistant individuals. This is possibly connected with the HLA system, which is directly involved in adaptive immune response formation. HLA molecule is responsible for the presentation of peptides to T-lymphocytes, which initiates the response of different immune system cells. HLA DRB1 is the most polymorphic of the HLA class II genes and therefore it can be used for individual identification [1].

The review of research results dealing with cystic echinococcosis also presents varying results. The research conducted on children in Russia demonstrates that HLA – DRB1*07, DQB1*09, DQB1*02 were associated with elevated risk of the progression of the disease and HLA- DQB1*02 and DRB1*03 with a higher risk of developing a complicated condition (superinfection of the cyst content with bacterial pathogens) [3]. Data from Lebanon allow the conclusion to be made that HLA-B*14 and HLA-DRB1*01 alleles are associated with lower risk of contracting the disease, while HLA-B*35 – with high risk; the researchers noted that their data are similar to the data from Russia [4]. The data from Saudi Arabia allow the conclusion to be drawn that, in the respective population, HLA-DR16 and HLA-DR7 alleles were associated with a higher risk of contracting the disease [5]. A study conducted in Yemen bears evidence that the HLA-DR16 allele is associated with increased risk of getting infected [6]. An Egyptian study also links HLA-DR3 with an increased risk of developing a complicated course of the disease [7]. A Turkish study in children population bears evidence that HLA-DR15 and HLA-B44 could be associated with the development of the disease, HLA-B18 and HLA-DR1 with resistance, meanwhile HLA-DR11 is associated with a high probability of recovery [8].

Materials and methods

The study analyses 144 patients with echinococcosis in the medical records available at the *Latvian Centre for Infectious Diseases* (LIC) for the time period from 1 January 1999 to 1 February 2015. During selection, 28 patients were not included in the study, because the diagnosis could not be considered to be verified in the presence of positive serology analyses alone, because cross-reaction with other flatworm parasites is possible. Meanwhile, other patients were excluded from the study group, because the finding of a simple cyst (radiologically no signs typical of echinococcosis are found) in the liver cannot be deemed to be echinococcosis, and furthermore, if it is not confirmed by serological analyses.

47 patients were included in the study, because 31 patients from the study group have died, meanwhile 38 patients did not wish to arrive to participate for various reasons. The patients were selected based on the following criteria: 1) proven case of parasitosis – positive serological finding and characteristic radiological findings (principally, ultrasound or computed tomography imaging data); 2) diagnosis occurred between the period of 1999 and 2015; 3) the patient had lived in Latvia for at least 15 years and was alive; 4) the patient gave their consent to participate in the study.

Determining of HLA DRB1; DQA1; DQB1 genotype was performed at the Joint Laboratory of Clinical Immunology and Immunogenetics of Riga Stradiņš University (RSU). Material from the data base of the Joint Laboratory of Clinical Immunology and Immunogenetics of RSU was used for the comparison of HLA test results, respectively, HLA of healthy

Table 1.
HLA-DRB1 alleles in patients and control group.

Alleles DRB1*	Patients with the Cystic echinococcosis alleles (n=58)	gene frequency	Odds Ratio	(p)	Controls alleles (n=200)	gene frequency
**01:01*	7	0.12	*0.31*	<0.022	31	0.15
**15:01*	3	0.05	*0.42*	<0.029	45	0.22
***17:01**	15	0.26	**2.32**	<0.044	14	0.07
***04:01**	7	0.12	**2.55**	<0.006	23	0.11
***11:01**	14	0.26	1.21	<0.551**	33	0.16
*13:01	5	0.08	0.71	<0.497**	29	0.14
*07:01	6	0.10	2.8	<0.137**	4	0.02
*08:01	1	0.01	0.18	<0.068**	14	0.07
*09:01	-	-	nd	-	2	0.01
*10:01	-	-	nd	-	5	0.02

Table 2.
Important HLA DRB1 allele combinations leading to more severe diasease
*While analysing HLA DQB1 alleles we cocluded that in cystic echinococcosis patients the most frequent allele was *03:02 (p<0,02).*

Alleles Group	*17:01/*11:01	*17:01/*13:01	*04:01/*11:01	*11:01/*13:01
All patients n=42 gf(P)&OR(*p*)	0.121	**0.075/8.11(0.037)**	**0.151/8.75(0.002)**	**0.090/4.90(0.044)**
Cystic echinococcosis patients (n=29) gf(P)&OR(*p*)	**0.189/3.66(0.029)**	0.054	**0.189/11.43(0.001)**	0.054
Control subjects n=100 gf	0.06	0.01	0.02	0.02

Table 3.
HLA-DQB1 alleles in patients and control group
*Regarding allele combinations we concluded that following lead to more severe disease: *02:01–2/*03:01 (p=0,033), *03:01/*03:02 (p=0,018) and *03:02/*06:02–8 (p=0,042), but protective was *03:01/*06:02–8 (p=0,05).*

Alleles DQB1*	Patients with the Cystic echinococcosis alleles (n=58)	Freq.	Odds Ratio	(p)	Controls (n=100) alleles (n=200)
*02:01–2	13	0.22	1.31	< 0.46**	28
*03:01	19	0.33	1.43	< 0.27**	39
***03:02**	11	0.19	**2.74**	< 0.02	12
*03:03	5	0.09	0.96	< 0.94**	14
*04:01–2	1	0.02	1.21	< 0.75**	9
*05:01	2	0.03	0.51	< 0.18**	25
*05:02–4	-	-	nd	nd	13
*06:01	2	0.03	0.48	< 0.33**	11
*06:02–8	5	0.09	0.76	< 0.42**	47

Table 4.
The most important allele combinations affecting course of the disease

alleles Group	*02:01–2/*03:01	*02:01–2/*05:01	*03:01/*03:02	*03:01/*06:02–8	*03:02/*06:02–8
All patients n=42 gf(P)&OR(*p*)	**0.106/3.84(0.047)**	0.045/0.75(0.459)	**0.151/17.68(0.0004)**	*0.136/0.89(0.06)*	**0.075/4.02(0.08)**
Cystic echinococcosis, patients (n=29) gf(P)&OR(*p*)	**0.135/5.05(0.033)**	0.027/0.44(0.390)	**0.108/12.0(0.018)**	*0.135/0.89(0.05)*	**0.108/5.94(0.042)**
Control subjects n=100 gf	0.030	0.060	0.01	0.15	0.02

blood donors was determined at the laboratory. Determining of HLA DRB1; DQA1; DQB1 genotype was performed at the Joint Laboratory of Clinical Immunology and Immunogenetics of Riga Stradiņš University (RSU). DNA is extracted from white blood cells by using the commercial *Qiagen* kit for DNA extraction from blood (*QIAamp® DNA Blood Mini Kit*), in accordance with the methodology approved by the manufacturer. Determining of HLA DRB1; DQA1; DQB1 genotype was performed by using low resolution PCR *(low resolution RT PCR-SSP Real-time PCR, qualitative analysis, melting curve analysis*), in accordance with the sequence specific parameters provided in the methodology of the manufacturer (*LLC " DNA Technology, Russia).* The main types of HLA DR/DQ alleles were identified.

Results

Incidence of DRB1, DQA1 and DQB1 alleles of HLA Class II were analysed during immunogenetic testing in all patients with echinococcosis, as well as separately in cystic and alveolar echinococcosis groups.

Material from the database of the Joint Laboratory of Clinical Immunology and Immunogenetics of RSU was used as the control group: HLA tests of healthy blood donors.

While analyzing HLA DRB1 gene alleles, one can conclude that in patients with cystic echinococcosis the most frequent are alleles *17:01 (p<0,044), *04:01 (p<0,006) but *01:01 (p<0.022) and *15:01 (p<0,029) are rare.

In cystic echinococcosis patients group allele combinations *17:01/*11:01 (p=0,029) and *04:01/*11:01 lead to more severe diasease presentation (p=0,001).

Discussion

One of the objectives and tasks of the study was to determine MHC HLA Class II alleles occurring among echinococcosis patients and their association with the severity of the disease.

It must be mentioned that literature data on the development of echinococcosis and immunogenetic factors of patients are limited and in the PubMed database only 10 publications could be used, because a certain number of studies were not available in English or Russian, as well as, for some studies, the original publications themselves were not available.

Analysis of the prevalence of HLA DRB1 gene alleles allows one to conclude that alleles *17:01 and *04:01 are more frequently found in patients with cystic echinococcosis. The association of allele *04:01 with increased risk of the disease has been described in China, however, it must be added that the Chinese publication refers to alveolar echinococcosis [1]. Alleles *01:01 and *15:01 rarely occur among the patients in the cystic echinococcosis group. Similar data on the protective action of allele *01:01 are mentioned in studies from Russia [1], Lebanon [4], Saudi Arabia [5] and Turkey [11]. It must be mentioned that contradicting data are available regarding allele *11:01 in a study conducted in Germany, where this allele is considered to be protective in the cases of alveolar echinococcosis [2], similar data have been obtained in Turkey [9], meanwhile the studies conducted in different European countries suggest that it has a protective character in the event of cystic echinococcosis [8]. It must be added that data similar to our data have been obtained from the nearest regions, for instance, Europe or Russia, while partially differing data come from different Asian countries and these differences are, potentially, due to genetic differences in race.

Analysis of the prevalence of HLA-DQB1 alleles leads one to the conclusion that allele *03:02, is credibly more frequent among cystic echinococcosis patients. Here our data contradict with literature data from Iran, where this allele is directly associated with a lower risk of cystic echinococcosis development [1], which could be explained by the fact that the population of this region in itself could have significant genetic differences from the Latvian population.

Analysis of the prevalence of HLA-DQA1 alleles leads one to the conclusion that allele *04:01, is credibly more frequent among cystic echinococcosis patients, while allele *01:01 occurs rarely. The available literature lacked information on the association of alleles HLA-DQA1 with severity of echinococcosis.

The data obtained by us here could be used in similar studies in other Baltic states, as well as European Union countries, which could expand the data base used for the detection of similarities and differences.

Immunogenetic data could prove significant for therapy planning in accordance with the individual characteristics of a patient, because no data on the optimal duration of therapy and whether the therapy can be terminated without facilitating the relapse of the infection are not currently available. It is known that there are patients, in whom the disease is progressing slowly and does not create serious complications, but it must be kept in mind that there is a group of patients, in whom even a brief suspension of therapy can lead to a rapid increase in the activity of parasitic process.

Conclusions

We can conclude that in the case of cystic echinococcosis a more severe course of a disease can be anticipated in the presence of HLA DRB1 alleles *17:01 and *04:01, DQB1 *03:02, DQA1*04:01. As well in the event of cystic echinococcosis HLA DRB1 alleles *01:01 and *15:01, DQA1 *01:01 can be considered as protective.

We think that our data are significant and further studies in larger patient group is needed to have more thorough information on impact on course of the disease and treatment strategies.

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