sciendo

PROCEEDINGS OF THE LATVIAN ACADEMY OF SCIENCES. Section B,
Vol. 73 (2019), No. 1 (718), pp. 10–16.

DOI: 10.2478/prolas-2019-0002

HLA CLASS II *-DRB, -DQA* AND *–DQB* GENOTYPES IN PERIPHERAL BLOOD SHOWS SHIFTS DURING THE COURSE OF SEPSIS

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Undeniably, sepsis is still a profoundly damaging and life-threatening condition for many individuals. With multiple changes in sepsis patients it is difficult to precisely classify an individual's response in sepsis as proinflammatory or immunosuppressed. The aim of this study was to investigate genetically determined predisposition to developed sepsis by analysis of distribution of human leukocyte antigen (HLA) class II genes. Samples from patients with sepsis were collected at Pauls Stradiņš Clinical University Hospital, Latvia, in an intensive care unit between October 2016 and May 2017. The study group included 62 patients with sepsis, who were genotyped for HLA-DR; DQ using real time polymerase chain reaction – sequence specific primer (RT PCR-SSP). As a control group, data of 100 individuals were taken from the genetic bank of RSU Joint Laboratory of Clinical Immunology and Immunogenetics. The summarised results showed that the frequency of alleles DRB1*04:01 *(OR = 5.54; 95% CI = 1.88–16.29);* DRB1*07:01 *(OR = 19.03; 95% CI = 2/37–152.82);* DQA1*05:01 *(OR = 14.17; 95% CI = 5.67–35.4); and* DQB1*02:01 *(OR = 50.00; 95% CI = 2.90–861.81) were significantly increased in patients with sepsis compared to the control group patients. The frequency of* DRB1*16:01 *(OR = 0.17, 95% CI = 0.04–0.59);* DRB1*17:01 *(OR = 0.04; 95% CI = 0.00–0.69);* DQA1*01:01 *(OR = 0.04; 95% CI = 0.00–0.31);* DQA1*01:02 *(OR = 0.03; 95% CI = 0.00–0.23);* DQB1*02:02 *(OR = 0.12; 95% CI = 0.03–0.42) alleles was lower in sepsis patients than in control subjects. The most frequent* HLA-DRB1/DQA1/DQB1 *haplotypes that was significantly increased in patients with sepsis were:* DRB1*01:01/DQA1*05:01/DQB1*03:01 *(OR = 12.6; 95% CI = 1.51–105.0;* p < *0.003). Sepsis patients with pneumonia and alleles and* DRB1 04:01; 07:01, DQB1 02:01 *had the highest mortality rate. Undoubtedly, our preliminary data showed that development of sepsis can be associated with alleles and haplotypes of HLA class II genes. For more precise conclusion the research should be continued to include a larger patient group.*

Key words: *genetic, human leukocyte antigen, sepsis, associated genes, major histocompatibility complex.*

INTRODUCTION

Sepsis is the leading cause of death in the intensive care unit and ranks in the top ten causes of death in general worldwide (Leentjens *et al*., 2013). The mortality rate of severe sepsis remains high (approximately 30%) despite improved clinical management algorithms (Levy *et al*., 2010).

Despite improvement in patient care, septic syndromes remain a public health challenge (Annane *et al*., 2005; Cazalis *et al*., 2014).

Sepsis development involves an active inflammatory reaction with massive release of proinflammatory cytokines. The release of these cytokines is associated with high mortality and development of organ dysfunction (Hotchkiss and Karl, 2003; Monneret *et al*., 2008; Hutchins *et al*., 2014).

Despite the extended laboratory and clinical study of sepsis, its diagnosis remains a clinical challenge. The initiation of sepsis activates many different biochemical and immunological pathways, which is expressed with alterations of many molecules of human tissues. The detection and the measurement of the concentration of such molecules, known as biomarkers, may be a diagnostic tool of great significance when the clinicians approach patients with suspected sepsis. Additionally, they may be used to predict outcome and therefore they may have a role in the monitoring of the response to therapy. There is a search for an ideal biomarker, which will enable sepsis patients to be identified in a timely manner and to prevent serious conditions and death (Payen *et al*., 2013).

A large number of genes that are known or predicted to have immunologic function reside alongside the human leukocyte antigen (HLA) genes, including HLA-II class (*DRB1; DQA1; DQB1*); HLA-III class (heat shock protein (HSP) molecules; complement factor B; complement components 2, 4A, and 4B; TNF-a and TNF-b (lymphotoxin) (Mato *et al.*, 2009).

The classical HLA loci are class I (HLA-A, -B, -C, -E, -F, and -G) and class II (HLA-DR, -DQ, -DM, and -DP) molecules identified for their role in presentation of antigen to CD8+ and CD4+ T cells, respectively. They are encoded by a 4-Mb region of human chromosome 6p21, which is recognised as the most variable region in the human genome and which has been designated the major histocompatibility complex (MHC) because of the important role played by class I and class II molecules in recognition of self versus nonself (Horton *et al.,* 2008).

The location of genes encoding classical HLA molecules in close proximity to so many other immune-related genes poses huge problems in trying to tease out the critical genetic/functional variants that might play a role in complex diseases such as sepsis (Burton *et al*., 2005; Blackwell *et al*., 2009).

The choice for study of the regions *DRB1, DQA1*, and *DQB1* was due to their crucial role in encoding the HLA class II molecules. HLA-DR consists of one α- and one β-chain, respectively encoded by one α-gene and four functional β-genes, called *HLA-DRB1*, *-DRB3, -DRB4*, and *-DRB5*. *HLA-DRB1* is constitutively always present with more than 100 different alleles. The individual *HLA-DRB* haplotypes correspond to the presence or absence of a specific combination between a *HLA-DRB1* gene and other *DRB* genes on each chromosome 6 (Choi *et al*., 2011).

HLA-DQ regions, especially the exons 2 and 3 that encode the α1 and β1 chains of the HLA-DQ subunits A1 and B1, are the regions that form the antigen cleft, where most of the genetic polymorphisms are concentrated (Shimokawa *et al*., 2016).

Technological, pharmacological, and surgical methods have improved the outcomes of many diseases. However, despite the efforts in developing diagnostic tools, such as scoring systems for predicting the outcome in case of critical illnesses, intensive care doctors are still unable to predict the outcome in all patients, especially for sepsis patients (Watson *et al*., 2003).

Extensive studies investigating the host responses during sepsis have revealed that the late phase of sepsis is dominated by a status of immune suppression with respect to missing or widespread depressed innate, as well as adaptive, immune defense mechanisms (Angus, 2010; Otto *et al*., 2011).

It is necessary to find additional approaches in prognostics and diagnostics to distinguish between infectious and non-infectious aetiology.

Moreover, the modern level of development of genetics and molecular biology has allowed an emphasis of the important role of genetics in the development of sepsis.

HLA genes have been known for a long time, but interest in this complex has constantly increased. Many infectious diseases are associated with genetic variation in the HLA class I and class II gene regions of the major histocompatibility complex (MHC) on chromosome 6p21.3 (Michalek *et al*., 2007; Eglite *et al*., 2010). HLA class I molecules present peptide antigens on the surface of almost all cells, whereas HLA class II molecules present antigens on the surface of antigen-presenting cells, such as dendritic cells, mononuclear phagocytes, and B cells (Hanna and Etzioni, 2014).

With the discovery of new technologies in molecular genetics, new infomation on genes and allelic specificity is presented every year (Anonymous, 2018a). Further still, the studies of contributions of HLA genes in a human body have almost exclusively focused on antigenic diversity and specificity. Certain genotypes regulate intercellular homeostasis, also associated with increased production of immune-stimulatory cytokines on exposure to pathogens. Sepsis is the result of the interaction between the microorganism and their products and the host factors released on response (cytokines and other mediators). This host response is an innate mechanism developed to protect the organism from harm, but in sepsis the response is in excess, with negative effects, leading to organ dysfunction and frequently to death (Jabandziev *et al*., 2014; Cajander *et al*., 2016). Several candidate genes have been identified as important in the inflammatory response and investigated in case-controlled studies. These are the *HLA DRB1* DQA1*DQB1** genes, positioned next to each other within the cluster of human leukocyteantigen class II genes.

Some previous studies showed that human leucocyte antigen class II (HLA II) alleles may have protective or risk importance in sepsis patients. Our objective was to identify HLA II class alleles of risk and protection in sepsis patients compared with control group patients.

These HLA association studies were conducted to identify disease-specific susceptibility (risk), and to identify protective markers that could be used in immunogenetic profiling, risk assessment and therapeutic decisions.

We summarise the evidence for a genetic susceptibility to develop the sepsis and unfavourable outcome of sepsis. We consider that the candidate genes are likely to be involved in the development of sepsis and based on genetic variability.

MATERIALS AND METHODS

Patient selection. This was a single-centre study at Pauls Stradiņš Clinical University Hospital, Latvia. The study group included patients (n = 62) who had sepsis and were enrolled during an eight-month period.

Sepsis criteria taken into consideration for including patients in the study were consecutive hospitalised patients who had two or more of the following signs during their first 24 hours in the units were diagnosed as systemic inflammatory response syndrome (SIRS): temperature of > 38 °C or < 36 °C, pulse rate of > 90 beats/min, respiratory rate of > 20 breaths/min or hyperventilation with partial pressure of arterial carbon dioxide of < 32 mmHg, or white blood cell (WBC) count of > 12 000 μL or < 4000 μL, or > 10% immature cells. Patients exhibiting two or more signs of SIRS with proven or suspected infection were diagnosed as sepsis and included in the study. Exclusion criteria were: < 18 years of age, acquired immunodeficiency syndrome, neutropenia (polymorphonuclear granulocyte count < 500 μL), or died within 24 hours after admission to the hospital, elected not to participate in the study, or declined treatment during the observation period (Angus, 2013).

Ethical approval for the study was obtained from the Ethics Committee (Rīga Stradiņš University). Written informed consent was obtained for each patient from the patient himself or from relatives.

DNA isolation. Genomic DNA for each individual meeting sepsis criteria was extracted from peripheral blood on admission day 1, by using QiagenQIAamp DNA kit reagents (Qiagen, Assay Technologies), as per the manufacturer's protocol (Anonymous, 2016).

HLA-DR and DQ genotyping low resolution by using RT-PCR. *HLA-DR-DQ* allele genotyping for simultaneous detection of *DRB1* 01:01* to *18:01* specificity, *DQA1*01:01*, *01:02, 01:03, 02:01, 03:01, 04:01, 05:01, 06:01*, and for *DQB1*02:01-02:02, *03:01-03:05, *04:01-04:02, *05:01-05:04,* and **06:01-06:08* was performed by RT-PCR qualitative multiplex analysis, using amplification with sequence-specific primer RT-PCR-SSP *HLA-DRB1; DQA1;DQB1* kits (DNA-Technology, Russia) (Anonymous, 2018b).

The reaction PCR mix (35 μl) included 5 μl DNA, and 10 μl PCR buffer. The PCR-Mix contained an internal control (DNA-IC). The IC is intended for PCR quality and sufficiency of DNA assurance. Registration and interpretation of the PCR results held in automatic mode was determined on a DTLite thermal Cycler (DNA-Technology, Russia). The *HLA-DQA1; DRB1*; and *DQB1* allele specificities for each sample were determined by the software version 7.3.5.84 and taking to account the total result from all tubes for each sample.

The control group included 100 randomly selected healthy unrelated Caucasians from the same area in Eastern Europe from the Rīga Stradiņš University, Joint Laboratory of Clinical Immunology and Immunogenetics. Inclusion criteria were: > 18 years of age, both sexes, no history of a septicemia and other chronic diseases.

Statistical analysis. Allelic frequencies of HLA alleles and haplotypes were compared between the patients and controls using the chi-square test and fisher's exact test. The odds ratio (OR) and confidence interval 95% (CI 95%) were calculated. The statistical analysis was conducted using SPSS (Statistical Package for the Social Sciences) (22.0 version) software. A p value < 0.05 was accepted as statistically significant.

RESULTS

We performed the study with 62 patients with sepsis, men 56.5% (n = 35) and women 43.5% (n = 27), the average age was 63.4 years (standard deviation 15.9). All patients were enrolled in the Pauls Stradiņš Clinical University Hospital of Latvia, in an intensive care unit between October 2016 and May 2017. The most common final clinical diagnosis was pneumonia 66% (n = 41), followed by complex soft tissue infections 13% (n = 8), surgical pathology 14.5% (n = 9) and urinary tract infection 6.5% (n = 4), The immunogenetic part of the study was done at Rīga Stradiņš University (RSU) Joint Laboratory of Clinical Immunology and Immunogenetics (JLCII). Sixty-two sepsis patients and control group of 100 healthy individuals were genotyped for *HLA-DRB1; DQB1* and *DQA1* using RT-PCR with sequence-specific primers.

The summarised results showed that frequencies of alleles *DRB1*04:01* (OR = 5.54; 95% CI = 1.88–16.29; $p = 0.001$); *DRB1*07:01* (OR = 19.03; 95% CI = 2.37–152.82; $p = 0.001$); *DQA1*05:01* (OR = 14.17; 95% CI = 5.67–35.4; $p < 0.001$); *DQB1*02:01* (OR = 50.00; 95% CI = 2.90–861.81; $p < 0.001$) were significantly increased in patients with sepsis compared to the control group patients. The frequencies of *DRB1*16:01* (OR = 0.17; 95% CI = 0.04–0.59; $p = 0.002$); *DRB1*17:01* (OR = 0.04; 95% CI = 0.00–0.69; $p = 0.001$); *DQA1*01:01* (OR = 0.04; 95% CI =

0.00–0.31; $p < 0.001$); *DQA1*01:02* (OR = 0.03; 95% CI = 0.00–0.23; $p < 0.001$); *DQB1*02:02* (OR = 0.12; 95% CI = 0.03–0.42; $p < 0.001$) alleles were lower in sepsis patients than in control subjects. Other alleles that were not statistically significant were not depicted here (Table 1).

The alleles that were significantly increased in patients with sepsis compared to the control group patients were analysed in respect to final clinical diagnosis of the sepsis patients with *DRB1*04:01* allele, pneumonia occurred in n = 12 (29.3%) patients and half of these patients died (n = 6, 14.7%); but surgical patology occurred in n = 2 (22.2%) patients and both of them died (n = 2, 22.2%). For patients with *DRB1*07:01* allele pneumonia was present in n = 4 (9.8%), complex soft tissue infection in n = 1 (12.5%), urinary tract infection in n = 3 (75.0%), surgical patology in n = 2 (22.0%). One patient with the *DRB1* 07:01* allele and surgical patology died (n = 1, 11.0%). For patients with *DQB1*02:01* allele, pneumonia was present in n = 7 (17.1%) and 3 patients died (n = 3, 8%), complex soft tissue infection in n = 4 (50.0%), and urinary tract infection in n = 1 (25.0%). For *DQB1*03:02*, pneumonia occurred in n = 7 (17.1%) patients, complex soft tissue infection in n = 1 (12.5%) and surgical patology in n = 2 (22.2%) (Table 2)

The most frequent *HLA-DRB1/DQA1/DQB1* haplotype that was significantly increased in patients with sepsis was *DRB1*01:01/DQA1*05:01/DQB1*03:01* (OR = 12.6; 95% CI = 1.51–105.0; p 0.003). Of the seven sepsis patients with this haplotype the most common final clinical diagnosis was pneumonia (n = 5, 12.2%), complex soft tissue infection (n = 1, 12.5%) and surgical patology (n = 1, 11.1%). Slightly increased values in sepsis patients were also observed for haplotypes
*DRB1*01:01/DQA1*03:01/DQB1*03:01* (OR = 8.33; 95% CI = 0.39–176.52; $p = 0.071$);
*DRB1*01:01/DQA1*03:01/DQB1*06:02-8* (OR = 8.33; 95% CI = 0.39–176.52; $p = 0.071$);
*DRB1*04:01/DQA1*05:01/DQB1*03:01* (OR = 8.33; 95% CI = 0.39–176.52; $p = 0.071$) and
*DRB1*07:01/DQA1*02:01/DQB1*03:03* (OR = 8.33; 95% CI = 0.39–176.52; $p = 0.071$), but they were not statistically significant. None of these haplotypes was observed in the control group, except for one patient with haplotype *DRB1*01:01/DQA1*05:01/DQB1*03:01* (Table 3).

DISCUSSION

Despite improvement in patient care, septic syndromes remain a public health challenge (Annane *et al*., 2005; Cazalis

Table 1

FREQUENCIES OF *DRB1*, DQA1** AND *DQB1** ALLELES IN SEPSIS AND CONTROL GROUP PATIENTS

Alleles	Sepsis patients, n = 62	Control subjects, n = 100	OR (95% CI)	*p*
*DRB1**				
*DRB1*04:01*	14 patients (22.6)	5 control subjects (5.0)	5.54 (1.88–16.29)	0.001
*DRB1*07:01*	10 patients (16.2)	1 (1.0)	19.03 (2.37–152.82)	0.001
*DRB1*16:01*	3(4.8)	23 (23.0)	0.17 (0.04–0.59)	0.002
*DRB1*17:01*	0	16 (16.0)	0.04 (0–0.69)	0.001
*DQA1**				
*DQA1*01:01*	1(1.6)	28 (28.0)	0.04 (0–0.31)	< 0.001
*DQA1*01:02*	1(1.6)	34 (34.0)	0.03 (0–0.23)	< 0.001
*DQA1*05:01*	32 (51.6)	7 (7.0)	14.17 (5.67–35.4)	< 0.001
*DQB1**				
*DQB1*02:01*	12 (19.4)	0	50.00 (2.90–861.81)	< 0.001
*DQB1*02:02*	3(4.8)	29 (29.0)	0.12 (0.03–0.42)	< 0.001
*DQB1*03:02*	10 (16.1)	7 (7.0)	2.55 (0.92–7.11)	0.065

n, the number of patients in the group (percent %); OR, odds ratio; CI, confidence interval

Table 2

FREQUENCY OF CLINICAL DIAGNOSES IN CONJUNCTION WITH SPECFIC ALLELES IN SEPSIS PATIENTS

Alleles	Pneumonia	Complex soft tissue infection	Urinary tract infection	Surgical pathology	Total
*DRB1*04:01*	n = 12 (29.3%)	n = 0 (0%)	n = 0 (0%)	n = 2 (22.2%)	n = 14 (22.6%)
*DRB1*07:01*	n = 4 (9.8%)	n = 1 (12.5%)	n = 3 (75.0%)	n = 2 (22.2%)	n = 10 (16.1%)
*DQA1*05:01*	n = 18 (43.9%)	n = 6 (75.0%)	n = 2 (50.0%)	n = 6 (66.7%)	n = 32 (51.6%)
*DQB1*02:01*	n = 7 (17.1%)	n = 4 (50.0%)	n = 1 (25.0%)	n = 0 (0%)	n = 12 (19.4%)
*DQB1*03:02*	n = 7 (17.1%)	n = 1 (12.5%)	n = 0 (0%)	n = 2 (22.2%)	n = 10 (16.1%)

n, the number of patients in the group (percent %)

Table 3

THE FREQUENCY OF *DRB1*/DQA1*/ DQB1** HAPLOTYPES IN PATIENTS WITH SEPSIS AND IN CONTROL GROUP PATIENTS

Haplotypes	Sepsis patients n = 62	Control subjects n = 100	OR (95% CI)	*p*
01:01/05:01*/03:01**	7(11.3)	1 (1.0)	12.6 (1.51–105.0)	0.003
01:01/03:01*/03:01**	2 (3.3)	0 (0)	8.33 (0.39–176.52)	0.071
01:01/03:01*/06:02-8**	2 (3.3)	0 (0)	8.33 (0.39–176.52)	0.071
04:01/05:01*/03:01**	2 (3.3)	0 (0)	8.33 (0.39–176.52)	0.071
07:01/02:01*/03:03**	2 (3.3)	0 (0)	8.33 (0.39–176.52)	0.071
12:01/05:01*/06:02-8**	1 (1.6)	0 (0)	-	-
13:01/05:01*/05:01**	1 (1.6)	0 (0)	-	-
15:01/02:01*/02:01**	1 (1.6)	0 (0)	-	-
16:01/05:01*/06:02-8**	1 (1.6)	0 (0)	-	-
15:01/05:01*/03:02**	1 (1.6)	0 (0)	-	-

n, the number of patients in the group (percent %); OR, odds ratio; CI, confidence interval

et al., 2014). Sepsis development involves an active inflammatory reaction with massive release of proinflammatory cytokines. The release of these cytokines is associated with high mortality and development of organ dysfunction (Hotchkiss and Karl, 2003; Monneret *et al*., 2008; Hutchins *et al*., 2014).

Research shows that genetic variation in human populations contributes to susceptibility to infectious disease (Burgner *et al*., 2006) and possibly also promoting development of sepsis.

HLA association studies have been conducted to identify disease-specific susceptibility (risk), and to find protective markers that can be used in immunogenetic profiling, risk assessment and therapeutic decisions. HLA class II molecules are highly polymorphic and play a pivotal role in superantigen presentation to T cells.

It is likely that the severity of sepsis might be influenced by the presence or absence of one HLA allele or more alleles forming haplotypes. The present study was conducted to investigate the association between *HLA-DRB1/DQA1/DQB1* alleles and haplotypes with susceptibility or protection to sepsis.

Our study focused attention on *HLA-DRB1, HLA-DQA1* and *HLA-DQB1* genes, which belong to a group of MHC genes called MHC class II genes. MHC class II genes provide instructions for making proteins that are present on the surface of certain immune system cells. These proteins attach to protein fragments (peptides) outside the cell. MHC class II proteins display these peptides to the immune system. If the immune system recognises the peptides as foreign (such as viral or bacterial peptides), it triggers a response to attack the invading viruses or bacteria. Each MHC class II gene has many possible variations, allowing the immune system to react to a wide range of foreign invaders.

Among the numerous markers that have been tested for their capacity to predict mortality in septic patients, the decreased expression on circulating monocytes of the major histocompatibility complex (MHC) class II molecule human leukocyte antigen-DR (HLA-DR) has proven to be a reliable predictor of adverse events (death, secondary nosocomial infections) in critically ill patients when measured 48 h after inaugural stress/injury (Pachot *et al*., 2005; Monneret *et al*., 2008; Cazalis *et al*., 2013).

In a 2013 retrospective study of the outcome in 999 patients with sepsis, the overall mortality was 31%, and the highest incidence of death (67.3%) was in the late phase, when multiple organ dysfunction developed (Cajander *et al*., 2013). Nevertheless, studies on drugs aimed to prevent this cytokine storm in sepsis patients have been inconclusive (Fisher *et al*., 1996; Monneret and Venet, 2015).

In one study, for example, downregulation of monocyte human leukocyte antigen-DR surface expression (mHLA-DR) measured by flow cytometry was postulated as a general biomarker of sepsis-induced immunosuppression and acted as an independent predictor of nosocomial infections (Landelle *et al*., 2010).

However, the use of mHLA-DR as a marker of immunosuppression has not yet been sufficiently evaluated in large multicenter studies of patients with sepsis, and this is most likely due to pre-analytical requirements and limitations in specimen handling (Cajander *et al*., 2013).

Our research results also showed that four of the *HLA-DRB1*, three of the *HLA-DQA1* and two of the *HLA-DQB1* alelles were significantly increased in patients with sepsis. Also, the most common diagnosis in patients with these alleles was pneumonia. There was a higher mortality rate in sepsis patients with pneumonia and certain alleles (*DRB1 04:01; 07:01, DQB1 02:01*). Therefore, it is important to identify sepsis in the first hours and to begin rapid antibacterial therapy to prevent mortality.

Research has shown that a large number of genes that are known or predicted to have immunologic function reside alongside the HLA genes, including HLA class II

(*DRB1/DQA1/DQB1*) (Kumpf, 2008). Genes involved in the immune response are the most numerous and the most diverse in the human genome (Kuniholm *et al*., 2016).

In our study the polymorphism of the human leucocyte antigen HLA class II-related haplotypes (*HLA-DRB1-DQA1-DQB1*) were investigated in sepsis patients and compared with a control group. In our opinion, it is very important that only one haplotype HLA-*DRB1*01:01/DQA1*05:01/DQB1*03:01* was significantly increased in patients with sepsis compared with control group patients. No other haplotypes were observed in sepsis patients.

Frequencies of several specific HLA II class alleles significantly differed between sepsis and control patients and the most clinical diagnosis was pneumonia with higher mortality, followed by complex soft tissue infections. Possibly, the development of sepsis may be associated with alleles of HLA class II genes.

For more precise conclusions the research should be continued with a larger patient group.

Limitation of the study. The findings of this study have to be taken wih caution since the sample size was relatively small to draw definitive conclusions. These results need to be confirmed prospectively in a large population.

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Received 28 August 2017
Accepted in the final form 17 December 2018

HLA II KLASES *-DRB*, *-DQA* UN *-DQB* GĒNU GENOTIPISKĀS IZMAIŅAS PERIFĒRAJĀS ASINĪS PACIENTIEM AR SEPSI

Sepse joprojām ir dzīvībai bīstams stāvoklis daudziem cilvēkiem. Mūsu pētījuma mērķis bija noskaidrot ģenētisko predispozīciju sepses attīstībai, analizējot cilvēka leikocītu antigēnu (HLA) II klases gēnu izplatību. Pētījumā tika iekļauti pacienti ar sepsi, kas stacionēti Paula Stradiņa klīniskajā universitātes slimnīcā laika periodā no 2016. gada oktobra līdz 2017. gada maijam. Pētījumā tika iekļauti 62 sepses pacienti, kuriem tika noteikti HLA II klases *-DR* un *-DQ* gēnu varianti izmantojot reālā laika polimerāzes ķēdes reakciju (RT PCR). Kontroles grupā bija 100 veseli indivīdi. Apkopotie rezultāti uzrādīja, ka alēles *DRB1*04:01* (OR = 5.54; 95% CI = 1.88–16.29); *DRB1*07:01* (OR = 19.03; 95% CI = 2/37–152.82); *DQA1*05:01* (OR = 14.17; 95% CI = 5.67–35.4); *DQB1*02:01* (OR = 50.00; 95% CI = 2.90–861.81) bija ievērojami palielinātas pacientiem ar sepsi salīdzinot ar kontroles grupas indivīdiem. Turpretī sekojošo alēļu — *DRB1*16:01* (OR = 0.17, 95% CI = 0.04–0.59); *DRB1*17:01* (OR = 0.04; 95% CI = 0.00–0.69); *DQA1*01:01* (OR = 0.04; 95% CI = 0.00–0.31); *DQA1*01:02* (OR = 0.03; 95% CI = 0.00–0.23); *DQB1*02:02* (OR = 0.12; 95% CI = 0.03–0.42) — biežums bija ievērojami zemāks tieši sepses pacientiem nekā kontroles grupai. Sepses pacientiem ievērojami palielināts bija haplotips *DRB1*01:01/DQA1*05:01/DQB1*03:01* (OR = 12.6; 95% CI = 1.51–105.0; $p < 0.003$), salīdzinot ar kontroles grupu. Pacientiem ar pneimoniju un konkrētām alēlēm — *DRB1*04:01; 07:01, DQB1*02:01* — novēroja augstāko mirstību. Neapšaubāmi, mūsu sākotnējie dati liecina, ka sepses attīstība var būt saistīta ar HLA II klases gēnu alēlēm. Lai iegūtu precīzākus secinājumus, pētniecību ir nepieciešams turpināt un sepses pacientu grupa ir jāpalielina.