ORIGINAL ARTICLE

HLA-DRB1 allele distribution among children with rheumatic heart disease in Haji Adam Malik Hospital Medan, Indonesia

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ABSTRACT

Rheumatic heart disease (RHD) is influenced by genetic factor, microorganism's virulence, and environmental factor. The aim of this study was to determine human leukocyte (HLA)-DRB1 allele among children with RHD in Medan, Indonesia.

Methods An observational study was conducted at the Department of Child Health, Haji Adam Malik Hospital Medan from April to June 2017. Inclusion criteria were children aged 5-18 years diagnosed with RHD. Children with concomitant congenital heart disease were excluded. HLA-DRB1 alleles were analyzed using the PCR sequence-specific priming (SSP) technique. Statistical analysis was done using computer software.

Results A total of 62 children were enrolled. The mean age of children was 12.6 (SD 3.44) years; 33 (53.2%) were male. The most dominant allele was HLA-DRB1*12, followed by HLA-DRB1*15.

Conclusion It is proven in this research that RHD is influenced by genetic factor with HLA-DRB1*12 allele found to be the most common allele in children with RHD in Medan, Indonesia.

Key words: cardiology, human leukocyte antigen, paediatric, RHD

INTRODUCTION

Rheumatic heart disease (RHD) is still the most common acquired heart disease worldwide. It causes permanent cardiac valve damage and leads to more severe conditions such as congestive heart disease, stroke, endocarditis, and death (1,2). Mortality rate from RHD is approximately 3.3%, annually. In Asia, RHD kills 356,000 – 542,000 patients every year (3,4). Rheumatic heart disease is a complex disease which is influenced by genetic factor, microorganism's virulence, and environmental factor (5).

An epidemiological study from 2009 found a relationship between genetic factor and RHD (6). Some human leukocyte antigen alleles are related to RHD (6). HLA-DR7 was reported to be a risk factor of RHD (2). A recent study in Uganda showed HLA alleles distribution in patients with RHD (7). The most common allele was HLA-DR11, which was found in 31.3% patients (7). Only 10.7% of healthy subjects in the study possessed HLA-DR11 allele (7).

Study regarding genetic factor, particularly HLA-DR alleles, and its relationship with RHD in Asia is scarce. Our study's goal was to provide the first data of HLA-DRB1 allele distribution among children with RHD in Medan, Indonesia as additional information for further investigation about the role of genetic factor in RHD.

PATIENTS AND METHODS

Patients and study design

An observational study was conducted in the Department of Child Health, Haji Adam Malik Hospital Medan (Indonesia) from April to June 2017. Patients were enrolled using consecutive sampling method. Inclusion criteria were children aged 5-18 years diagnosed with RHD. Children with concomitant congenital heart disease based on echocardiography evaluation were excluded. Children or proxies were interviewed to obtain gender and age data.

Informed consent was obtained before conducting the procedure.

An approval of the Ethics Committee, School of Medicine, Universitas Sumatera Utara was obtained.

Methods

Blood samples were drawn and genetic analysis was conducted for each sample. HLA-DRB1 alleles were analyzed using the PCR sequence-specific priming (SSP) technique using Olerup SSP® HLA typing kit (CareDx, Inc., Brisbane, California). Sample handling was conducted in Multidiscipline Laboratory Universitas Sumatera Utara.

Statistical analysis

Statistical analysis was done using computer software. Numerical data were presented in mean and standard deviation, whilst categorical ones in frequency and percentages.

RESULTS

A total of 62 children were enrolled in this study. Mean age of the children was 12.6 (SD 3.44) years with age range of 9-16. Males were more dominant, 33 (53.2%).

The most common allele was allele 12 (44 children), followed by allele 15 (32 children). The rarest allele was allele 09 (one child), followed by allele 04 (two children) (Figure 1).
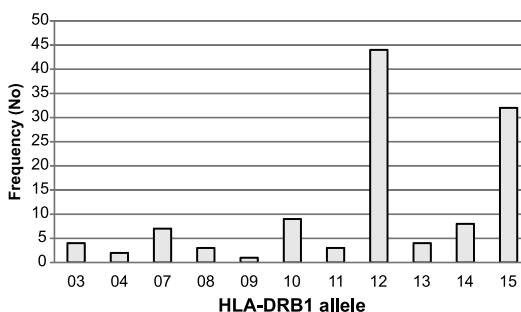

Figure 1. HLA-DRB1 alleles distribution in 62 children with rheumatic heart disease

DISCUSSION

The RHD is common in developing countries and increases their national economic and epidemiologic burdens (2). In the next 5 to 20 years, approximately 15 million children and adolescents will suffer from RHD, and most of them require recurrent hospital admission and, not uncommonly, cardiothoracic surgery (8). The RHD is most prevalent in population between 5 and 16 years, hampering the crucial developmental period of a generation (9). As observed in this study, the mean age of RHD sufferer was 12.6 years. No

gender predilection is reported in the occurrence of RHD (10), but in our study male patients were slightly more dominant.

HLA plays an essential role in shaping one's immune system by regulating the antigen presentation of peptides and immune response (11). Therefore, it is suspected to be involved in auto-immune disease pathogenesis. Some autoimmune diseases such as Behcet's disease, celiac disease, and rheumatoid arthritis are related to HLA (11,12). The gene which codes a particular HLA protein in humans has several epitopes (12). The shared epitope for the HLA is passed on from generation to generation in an exclusive population. This is the reason why several populations are prone to a specific autoimmune disease, while some other are not. This proposed mechanism is called epitope hypothesis (13).

Similar condition is proposed in RHD. Host's genetic susceptibility has been suspected as one of the culprit of RHD (14,15). RHD is caused by immune response toward the Group A *Streptococcus* (GAS) infection (14). The microorganism often infects upper respiratory tract or skin. Several strains of GAS have surface proteins, especially protein M, which have similar molecular structure with cardiomyosin, tropomyosin, keratin, laminin, vimentin, and several cardiac valve proteins (10). Protein M is processed by HLA and presented to immune cells. Immune reaction is then triggered to eliminate the microorganism. Unfortunately, cross reaction between protein M and body's proteins also induces inflammation and damage in cardiac tissues (16). This pathogenesis confirms the concept of autoimmunity as the basis of RHD (2,17).

A study in India from 2010 to 2011 showed that several types of HLA were associated with RHD and the HLA type was different with other region's report (18). It can be inferred that HLA allele distribution in RHD patients is different in each ethnicity. HLA-DR7 allele is the most common associated genetic predisposition for RHD. The allele is highly found in patients with RHD from Brazil-Mullatos and Brazil-Caucasians ethnicities (19). A study from India in 1986 showed a positive association between HLA-DR2 allele and RHD. On the other hand, HLA-DR2 allele was negatively associated with the disease (20). In Turkey, the presence of HLA-DR11 and HLA-A10 increased the risk of RHD (21). In Uganda, it was HLA-DR11 allele which increased the risk of RHD (8).

This is the first study to determine HLA-DRB1 allele distribution among children and adolescents with RHD. In our study, the most dominant allele is HLA-DRB1*12, followed by HLA-DRB1* 15. Those findings are different from other studies from several regions and ethnicities. This is possibly caused by minor rearrangement in gene sequence at first. The rearrangement is induced by epigenetic events and accumulates as time goes by. This process creates different phenotypes from the ancient gene. The new gene sequence is then inherited and carried by next generation of specific populations (22).

A population based study is mandatory to extrapolate the result of this study, as this is a pilot hospital based study. Subjects from other regions of Indonesia should be involved to achieve more representative results.

In conclusion, it is proven in this research that RHD is influenced by genetic factor with HLA-DRB1*12 allele found to be the most common allele in children with RHD in Medan, Indonesia.

FUNDING

TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

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