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Characterization of Secondary Autoimmune Etiologies Related to Rheumatic Fever

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Abstract

The rheumatic fever (RF) is a systemic inflammatory autoimmune disease, which occurs after a pharyngeal infection by *Streptococcus pyogenes*. The disease can cause arthritis, *erythema marginatum*, subcutaneous nodules, carditis and Sydenham's chorea. The signs and symptoms of the disease are caused by the immune response against *Streptococcus sp.*, however, only individuals with a genetic predisposition may be affected by this disease. It was noted in some cases, where the person with RF also have positive diagnostic of other autoimmune diseases such as systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), and Hashimoto's thyroiditis (HT). It has been reported in literature, the similarity between etiological mechanisms of RF and Tourette's syndrome (TS). This study aimed to characterize the autoimmune diseases related to RF, analyzing the etiological mechanisms, immune responses, and genetics involvement within those diseases, and establishing possible relationships in genetic level, between conditions. The results revealed that Human Leukocyte Antigen (HLA) genes system play a major role in the predisposition to develop those cited diseases, and in particular, HLA DR3 can be linked to exacerbation in cellular immune response.

Keywords: Rheumatic fever; autoimmune diseases; HLA genes sytem

Abbreviations

RF: Rheumatic Fever;

SLE: Systemic Lupus Erythematosus;

APS: Antiphospholipid syndrome;

HT: Hashimoto's Thyroiditis;

TS: Tourette's Syndrome;

HLA: Human Leukocyte Antigen

Introduction

Rheumatic fever (RF) is a systemic inflammatory disease, immune-mediated, which occurs as a late consequence of a pharyngeal infection by beta hemolytic streptococcus group A [1].

The origin of the disease is related to cross-reaction called molecular mimicry. Its manifestations are varied, as polyarthritis, carditis, Sydenham's chorea (characterized by motor tics and nervous), subcutaneous nodules and *erythema marginatum* [2].

Worldwide, it is estimated that, each year, occurs about 500,000 new cases of RF, especially in developing countries [2]. Usually affects individuals of both sexes, within school age, of any race, anywhere in the world [3], and in only 20% of cases, occurs in adults [1].

Mostly, in the first RF attacks (about 75%) arthritis manifestations are correlated. The carditis-related events occurs in 40% to 50% of cases; chorea 15% of the cases; and subcutaneous nodules and *erythema marginatum* in less than 10%. Thus, the rheumatic-related heart disease is more common in children and arthritis predominates in adults [1].

The immune response to streptococcus is responsible for the appearance of clinical manifestations [1-4] and attributed to these manifestations, different immunological mechanisms [5]. A humoral immune response triggers arthritis and chorea and the skin and cardiac events are caused by a cellular immune response, however, the acute phase of cardiac complications is also involved in an immune response, mediated by antibodies [4,5].

The patient who develops rheumatic fever has a genetic and immunological predisposition that makes it prone to the occurrence of other autoimmune diseases [6], so it is not unusual to find other autoimmune disease within patients with RF [6.9].

Some studies concerning autoimmune diseases, display similarities within each other, either in their relations with the pathogenic findings of RF, or regarding clinical symptoms presented [6,9].

This study aims to describe the associations between rheumatic fever and other autoimmune diseases, correlating similarities within pathological mechanisms among autoimmune diseases, as well its immunobiological response, in order to establish possible relationships between different etiological conditions that occurs concomitant to RF disease.

Materials and Methods

The present work is an exploratory, descriptive study which used, primarily, the following databases: Medical Literature Analysis and Retrieval System Online (MEDLINE), Scientific Electronic Library Online (SciELO), Latin American and Caribbean Health Sciences (LILACS), Virtual Health Library (VHL) and National Center for Biotechnology Information (NCBI).

The search for articles consisted of two steps. First were researched articles that addressed issues related to "Rheumatic Fever" and "Autoimmune Diseases". After the selection, articles and data collection were based on articles with autoimmune diseases associated with rheumatic fever, which were found in the first moment of the search. In both stages of the search, it has been used the descriptor both in Portuguese, as well as in English.

For inclusion, the articles should be in the public domain and available in electronic format. Books, texts, articles in journals not indexed, editorials and opinion articles were excluded from the search.

The analysis of the results was based on the 2001- early 2015 publications.

The work consisted of reading of full articles, using the data analyzed to the correlate conditions proposed in this study.

Results

Systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), Hashimoto's thyroiditis (HT) and Tourette syndrome (TS) have been described in the literature in association with RF [6-9].

Thus, in RF there are humoral and cellular immune occurrences [4,5], HT and in SLE disease lead also to both responses [12, 13]. Whereas, in TS and APS prevail only humoral responses [7,14].

Regarding RF and TS conditions, both display high correlation at pathological phenotypic level due to their common etiological agent, after a streptococcal infection, predisposing individuals to genetically alterations in Human Leukocyte Antigen (HLA) system [1-4, 7].

Throughout analyses of published literature, it was possible to establish that the genetic trait illustrated above was the most relevant relationship between RF and genetic dysfunction within the autoimmune diseases, portrayed so far. Interesting molecular alterations were described at the Human Leukocyte Antigen (HLA) system genes. This relationship found prospecting recent references is discussed below. The data analyzed in this work is summarized in Table 1.

Table 1. Description of HLA alleles related to each one of the autoimmune condition described in the study.

Condition	HLA related	Reference
RF	B1*07, DR2, DR3, DR4, DR7, DR9 e DR53	[5], [15]
SLE	A1, A10, B8, B18, DR2 e DR3	[8], [16]
APS	DR4, DR7 e DR53	[14]
HT	DR3, DR4 e DR5	[18]
TS	no	[19]

Discussion

Despite RF conditions occur after a pharyngeal infection by *Streptococcus pyogenes* [1-4], the literature infers that only people with a genetic predisposition may develop manifestations of rheumatic fever (RF) [6].

The predisposition to RF development is linked to HLA gene family [5], as well as in the most autoimmune diseases cited in this study [12 -14].

An important event on the relationship between HLA genes and RF, is the fact that there is variability in the expression of alleles in individuals with RF, and this characteristic is related to ethnic factors [21]. The Caucasian population of the United States with RF, it is described to have the predominant expression of HLA-DR4 and HLA-DR9 [20]. In the African American population with the disease, the prevalence of HLA-DR2 is higher [21]. In Brazil, the majority of studied individuals show expression of HLA-DR7, HLA-DR53 and HLA-DRB1*7 alleles. The HLA-DR3 allele is also present in individuals with RF, especially those who develop rheumatic heart disease [15].

In the case of systemic lupus erythematosus (SLE), complications occur as a result of production of antibodies against double-stranded DNA, and is strongly related with genetic predisposition, and often also with environmental and hormonal factors. The HLA alleles that are associated with SLE are: HLA-A10, HLA-B18, HLA-DR2, HLA-DR3, HLA-A1 and HLA-B8. The HLA-A10 and HLA-B18 alleles are related to a failure in the complement system. Thus HLA-DR3, HLA-B8, and HLA-A1 are closely related to the exacerbation of cellular immune response [16].

In the antiphospholipid antibody syndrome (APS), the complications are caused by the production of antibodies that react with membrane-phospholipids present at platelets, or at endothelial tissue, causing thrombotic events [14]. Despite, until the moment, no correlation was described between the APS and infection by *S. pyogenes*, some evidence was described associating that syndrome as a main trigger in the development of RF in committed patients [17]. One important finding which supports this the fact is that the production of anticardiolipin antibodies occurs in APS [14]. Tamura and colleagues (2002) detected the presence of anticardiolipin antibodies in 8 of 13 patients with reactive arthritis due to streptococcal infection, that suggests a close relation regarding these production of antibodies and streptococcal Infection [17]. In another study of patients with the syndrome, sera of 16.6% of the patients recognized M protein, which is one of the *S. pyogenes* antigenic structures. These facts demonstrate that there may be a causal relationship between streptococcal infection and the APS [9]. As observed through literature, the HLA alleles present in the APS, can be inferred as HLA-DR4, HLA-DR7 and HLA-DR53 [14].

In Hashimoto's thyroiditis (HT), complications occur due to a humoral and cellular immune response, which is characterized by infiltration of autoreactive T cells in the thyroid gland, which compromises thyroidal hormones production [12]. The HLA alleles associated with the disease are HLA-DR3, HLA-DR4 and HLA-DR5 [18].

Tourette's syndrome (TS) is an autoimmune response caused by autoantibodies that react with the nervous system of the affected person [7]. Although there is a great similarity regarding an etiological point of view between RF and TS, considering that both are triggered by a previous infection in oropharynx with *S. pyogenes*, HLA alleles are not related to the immune response developed in the TS, as is positive described in the RF [19]. However, the presence of cell surface antigen on B lymphocytes types D8/17, was detected at high levels, either in patients with RF, as in patients with TS [7, 20]. Although TS displays some similarities to rheumatoid chorea, it was observed that the expression of D8/17 is not limited only to patients with rheumatic chorea, and is representative in patients with other RF complications, as carditis [21]. For comprehensive understanding, refer to Table 1 described above.

Conclusion

By observing alleles of each described autoimmune diseases it is fair to affirm that individuals with RF, share important genetic alterations in alleles of the HLA genes system. With exception of TS, all annotated disorders in this study have a genetic similarity in the HLA system.

Within the data presented in this study was not possible to associate the humoral immune response of some diseases to its inferred genetic alterations. Although it is known that gene profile in these diseases plays a critical role in the maintenance of the disease itself, and specially its progression. However, as regards the cellular immune response, HLA-DR3 allele appears to be present in all diseases that have some immune response mediated by T cells (RF, SLE, and HT). However, it is not possible to assert that HLA-DR3 is an autoimmunity marker, because, so far, there is no consensus in the literature regarding the role of these alleles as a trigger in exacerbated responses, or neither if it represents a *middlemen*, which increases

and favors the sensitivity of T cells into recognize and attack self-structures; or even what are the mechanistic events related to T cells modulation.

After analyzing the data published is clear the relationship of other autoimmune diseases with RF, not only in phenotypic matter, but also in genotypic matter. These findings may help to endorse a unique clinical point of view upon RF carriers, as well as upon individuals with any other autoimmune etiology, subsidizing the promotion of early diagnosis recognition, for different expressed conditions. The genetic similarity observed among these disorders is a relevant etiological trait and which, if early notice, may interweaves present and future descriptions of RF conditions.

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