Immunogenic aspect of the chronic tonsillitis associated with articular syndrome

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Abstract

Background: There are proposed various methods of treatment of articular syndrome associated with chronic tonsillitis (CT), however, in most cases the desired effect is not reached. The insufficient effectiveness of the treatment measures is, to a certain extent, subject to the underestimation of the immunogenetic role of the etiologic and pathogenetic character of these diseases. Recent years yielded obvious results in studying the correlation between the disease and the histocompatibility complex antigens – HLA (Human Leukocyte Antigens). At the foundation of the complex is the phenomenon of its predisposition to various diseases. In the curative approach of chronic tonsillitis, the presence of certain classes of HLA complex genes indicate the need for an early aggressive therapy. It deeply involves into the disease pathogenesis, coding the therapy evolution, prognosis and effects. In order to evaluate the impact of HLA class I antigenic determinants (A and B) on the clinical presentation, evolution and treatment strategy in patients with decompensated chronic tonsillitis associated with the articular syndrome (PSRA or ARF), we observed 101 adult patients aged 16-60 years, clinically and instrumentally diagnosed with decompensated chronic tonsillitis (CT): 50 patients had received conservative treatment and 51 patients were treated surgically.
Conclusions: The study of the major antigens has not found an association of HLA class I (A, B) with ARF and rheumatic heart disease (RHD).
Key words: chronic tonsillitis, articular syndrome, arthritis, antigens.

According to The American Academy of Otolaryngology - Head and Neck Surgery, chronic tonsillitis (CT) is: an entity unresponsive to medical therapy; which is associated with halitosis; with clinical presentation of recurrent tonsillitis (RT) at persons carrying beta hemolytic streptococcus class A (BHSA); with absence of adequate response to antimicrobial therapy and with surgery indication (tonsillectomy) [10].

Chronic inflammation of the tonsils is one of the most common otorhinolaryngology diseases. About 10-50% of people complain of symptoms of chronic tonsillitis [2, 3].

The study conducted among the population of the Republic of Moldova in 2008-2009 (1500 people were examined in 16 districts and 38 villages), found the most common disorders of the pharynx: CT and chronic pharyngitis. The authors introduced the term chronic amigdalo-pharyngitis in the daily use of doctors, which contributes to a better selection of patients for those treatments [1].

Determining the prevalence of CT was performed by examining a group of 1371 children (967 children from urban area and 404 children from rural area of the Republic of Moldova). CT prevalence in children is 7.7%, does not depend on sex, and is more common at the age of 12-13 years and in urban areas [4, 5].

BHSA infection complications are classified as non-suppurative and suppurative. Acute rheumatic fever (ARF), post-streptococcal reactive arthritis (PSRA) and acute glomerulonephritis are major non-suppurative complications

occurring generally after 1-3 weeks after the beginning of BHSA infection.

PSRA is a clinical syndrome without diagnostic criteria and clear treatment recommendations [34]. PSRA was defined as a non-suppurative inflammatory arthritis in two or more joints, which develops during or shortly after a streptococcal infection, located remotely, at a patient without Jones criteria for ARF diagnosis [18, 34, 40].

Studies conducted among both children and adults postulated the relationship between streptococcal tonsillitis and PSRA [11,14]. According to some studies, PSRA occurs most often in young adults [13]. Recurrent, severe and prolonged arthritis are important PSRA characteristics at adults [11].

ARF is an autoimmune disease caused by gram-positive bacteria Streptococcus pyogenes after an untreated oropharyngeal infection at children genetically susceptible. This multi-system disorder is characterized by involvment of heart, joints, central nervous system, subcutaneous tissue and skin, but, except the heart, the other organs are affected transiently [39, 41, 44, 45].

There is no "gold standard" and no specific test to diagnose ARF, therefore, the diagnosis is arbitrary and empirical, especially in adults over the age of 25 years [22, 33, 37]. The diagnosis criteria of ARF were developed and published by Jones TD in 1944 [27, 32, 37, 44, 45], and till now are extremely important in the diagnosis, study and management of this injury [37]. The changes and subsequent updates of ARF criteria, published in 1965, 1984, 1992 and 2002, have concretized and completed major manifestations, have simplified minor occurences, have removed the ambiguity and have detailed all criteria, have underlined the importance of the preceding streptococcal infections with the purpose of appropriate diagnosis of the initial stroke, the recurrent stroke, and minimizing the overdiagnosis of this condition, especially in countries with reduced incidence of ARF [22, 27, 32, 33, 37].

PSRA treatment represents the impovement of arthritis symptoms and eradication of streptococcal infection by administration of non-steroidal anti-inflammatories and antibiotics [41]. Early tonsillectomy is a viable treatment for patients with PSRA after strep throat [13]. According to the AHA, patients with PSRA are recommended to be under surveillance for several months and under echocardiographic monitoring in order to detect a possible further development of carditis, which may be atypical ("quiet"). One of the recommendations is the secondary prophylactic administration of antibiotics to patients with PSRA for up to 1 year and, if the carditis is not determined, prophylaxis may be interrupted. If the carditis is diagnosed, the patient is considered to have ARF and he must continue getting the long-drawn secondary prophylaxis treatment with antibiotics [14, 17, 18].

ARF treatment is performed in several directions, the most commonly used are [29, 41, 44]: the treatment of streptococcal infection with penicillin G, a first-line anti-inflammatory treatment with acetyl salicylic acid in uncomplicated cases and with corticosteroids in more severe cases.

ARF prophylaxis comprises several aspects: elimination of risk factors associated with BHSA, detection and proper treatment of throat infections with BHSA with penicillin G (primary prevention), detection of healthy carriers of strep that are treated as symptomatic patients (primary prevention), prevention of complications, in particular of carditis, in patients with ARF (secondary prevention) [30, 31].

Effective treatment of tonsillitis with BHSA reduces the risk of ARF by approximately 80-90%, but BHSA remains present in the pharynx in about 10% of cases, even after a proper treatment [29].

There are proposed various methods of treatment of CT: conservative treatment (local, general, prophylactic) and surgery (tonsillectomy). But in most cases the desired effect is not achieved. In addition, at this stage doctors demonstrate an explainable prudence regarding tonsillectomy, especially in children, when the physiological function of these lymphoid organs is maximal [2, 3, 19, 46].

The low efficiency of treatment measures is conditioned, to some extent, by the underestimation of the immunogenetic role of the etiopathogenic appearance of CT. In recent decades there were obtained obvious results in studying the correlation between CT and MHC- HLA antigen [38].

According to several recent studies, CT pathogenesis is complicated and diverse. Ethiopatogenic links between CT and other intercurrent diseases are not established. Studying the level of correlation between local immunological disorders and systemic immune processes, phenomena that are at the base of the immune response in the development zone of an isolated inflammatory process is important, at least from two points of view. On the one hand, these results will complement the vision of CT pathogenesis, and on the other hand, would give new impetus for the pathogenic treatment, serving also as a basis to form a fair outcome [6].

CT diagnosis is extremely difficult because both the onset and progression of the disease do not show specific clinical signs. The most common clinical manifestations of CT are obstructive hypertrophy of the tonsils (HT) and / or RT [37]. CT symptoms (painful and discrete sensations in the throat, non-disclosed sore throat, dysphagia, dry cough, bad breath, pharyngeal discomfort, sensation of a foreign body and discomfort in the throat, burning and dryness in the throat, low-grade fever, pain in the lymphatic submandibular nodes, pain in the joints) are also met in other diseases (pharyngitis, laryngitis, esophagitis, gastritis, sinusitis etc.) [6, 10, 37].

Therefore, CT diagnosis is based on a combination of clinical and laboratory data, and instrumental examinations.

The general algorithm of conduct in the diagnosis of CT includes: 1) collection of anamnesis (patient accusations, disease duration, angina incurred in the past, associated diseases), 2) clinical objective examination (local signs of CT, changes in the joints, changes in the cardiovascular, kidney systems), 3) paraclinic laboratory tests: general analysis of blood, urine summary, electrocardiogram, biochemical examination of the blood (bilirubin, alanine aminotransferase, aspartate aminotransferase, thymol test), inflammation samples (ESR, fibrinogen, C-reactive protein (CRP)), serology tests (ASLO), the examination of pharyngeal superficial exsudate, obtained from pads or fine needle aspiration (being significant

the presence of BHSA) and antibioticograma, consultation of an ENT doctor, pediatrician, rheumatologist, nephrologist and / or urologist, stomatologist [3, 7, 12, 16, 19 32].

Although the risk of infection depends on environmental conditions (exposure, season, geographical area) and individual variables (age, strength, immunity), the identification of the specific agent is of a significant importance for selecting the treatment, ensuring a rapid recovery and prevention of complications [19]. CT more often (42% of cases) is caused by infection with respiratory viruses (adenovirus, influenza virus, para-influenza virus, rhinovirus or respiratory syncytial virus), and in 30-40% of cases the cause is a bacterial infection [9, 10, 19]. Of all the microorganisms, the main ethiopatogenic agents in CT are BHSA (15 to 55.5% of cases), followed by Staphylococcus aureus [8, 12, 16, 40].

In the recent years, Staphylococcus aureus is considered the main pathogen responsible for CT [35]. According to the results of studies, the most common pathogen was Staphylococcus aureus (33%), followed by BHSA (30%), Streptococcus pneumoniae, Haemophilus influenzae, Escherichia coli, Pseudomonas aeruginosa and Streptococcus viridans [35]. According to another study, Staphylococcus aureus (30.3%), Haemophilus influenzae (15.5%) and Streptococcus pyogenes (14.4%) were the most frequently isolated from patients with CA [9].

Although the cultures of tonsil core compared with isolated cultures from superficial pharyngeal smears, provide a representative picture of the bacterial content in patients with CT and RT [15], in our study, the bacteriological analysis from the pharynx detected Streptococcus viridans in 56 (55.4%) cases, Staphylococcus aureus in 51 (50.5%) cases, Streptococcus pyogenes in 45 (44.6%) cases, BHSA in 17 (16.8%) cases, Streptococcus pneumoniae in 8 (7.9%) and other flora in 22 (21.8%) cases. It should be underlined that different combinations of determined pathogen agents were found in most cases – in 87 (86.1%) patients.

Several researchers have tried to determine the genetic susceptibility and protective immune responses for PSRA and ARF [21, 25, 28, 30]. Validation of HLA associations observed in various populations of the world can contribute to the development of cost-effective primary prevention strategies of these lesions [28]. It was observed a heterogeneity in terms of HLA alleles class I and II of susceptibility and/or protection in different studies in different geographical regions and ethnic groups, although associations with specific antigens have been reported [21, 25, 28, 30].

The study of major antigens did not find an association of HLA Class I (A, B and C) with ARF and RHD [23, 24, 31, 42]. In other studies in patients with CT, including decompensated CT, statistically significantly more often were found the antigens HLA-A2 and HLA-B12 [46]. Among children with mitral valve disease (MVD), compared to children in the control group, there was noted a significant increase in HLA-B5, and HLA-B49, HLA-B51 and HLA-B52 were found only in the control group and they have a protective role for these conditions [28].

Among mature people with ARF was also found a large increase, but statistically non-significant, of HLA-B5, compared to the control group, a statistically significant increase in HLA-A10 and HLA-B35 [36].

In different populations, the frequency of HLA-A10, HLA-Aw33 and HLA-B35 antigens is significantly higher in adult patients with ARF and / or RHD ($p<0.05$ and $P<0.01$, respectively). The frequency of HLA-A10 and HLA-DRw11 antigens in patients with RHD is significantly higher than in those with non-cardiac involvement ($p<0.05$ and $p<0.01$, respectively). On the other hand, the frequency of HLA-CH2 antigen is significantly higher in patients without RHD compared to those with RHD ($p<0.05$) [36].

The absence of a hereditary marker HLA class I in patients with RHD underlines the multiple and important factorial complexity in ARF pathogenesis, but does not exclude the role of genetic factors [42]. However, the susceptibility of RHD is mediated by HLA class II [43].

At patients in our study with chronic tonsillitis and articular syndrome, most frequently were diagnosed the following HLA Class A antigens (HLA-A2 – 44,6%, HLA-A28 – 41,6%, HLA-A24 – 23,8%, HLA-AX – 20,0%) and HLA class B (HLA-B35 – 31,7%, HLA-B44 – 17,8%, HLA-BY – 14,9%, HLA-B18 – 12,9%).

Therefore, the relationship between ARF and PSRA with HLA is contradictory and heterogeneous, and the sensitivity to ARF (and PSRA) is polygenic. Some diseases with poor initial association with the antigens HLA-A and HLA-B were found to have strong association with HLA-DR antigens. The strongest and most frequent association of ARF was proved to be with HLA-DR2, HLA-DR4 and HLA-DR7 phenotypes, and the PSRA – with HLA-DRB1 * 01 [14, 17, 23, 24, 39]. The relatively small number of patients tested and the differences in genetic background may partly explain the different results and the difficulty in the study of HLA alleles in identifying the same genetic susceptibility in different population. In order to understand completely the overall mechanism of genetic susceptibility, such studies need to be duplicated and validated in different ethnic populations, using a wider range of appropriate methods of analysis [28].

Currently, there are very few studies that estimate the role of the genetic system in the development of CT. Most studies provide additional information on genetic predisposition for MVD and protection genotypes in RHD. The results of several studies conducted in concordance to the hypothesis that the susceptibility to RHD is genetically determined, have found a possible association with antigens HLA class II (HLA-DR) and a weak one with antigens HLA class I (HLA-A, HLA-B and HLA-C) [26]. Estimation of HLA class I antigens found a statistically significant increase in HLA-B5 alleles in patients with RHD ($p=0.03$) compared to the control group, whereas the alleles HLA-B49 ($p=0.004$) and the HLA- B52 ($p=0.02$) were found only in the control group [28]. A recent case-control study compared the frequency of CHM class II, HLA-DR alleles between patients with and without RHD. The authors found a low genetic susceptibility of HLA-DR1 with RHD, while HLA-DR11 was associated with an increased risk for RHD [20].

According to specialized literature, the impact of tonsillectomy versus non-surgical treatment is modest [48]. However,

tonsillectomy reduces the symptoms of CT or RT in adults with remarkable effectiveness, resulting in a reduction in the number of episodes of sore throat and days with sore throat in children in the first year after surgery [48].

Conclusions

The study of the major antigens has not found an association of HLA class I (A, B) with ARF and rheumatic heart disease (RHD).

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