

HOW IMMUNE IS THE CARDIOVASCULAR SYSTEM? THE POINT OF VIEW OF A PEDIATRIC CARDIOLOGIST

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Immune mechanisms are increasingly identified in a variety of disease states of heart and vessels in children. All components of the heart and vessels can be the target of the immune process. This review will not discuss the immune deficiencies and their repercussion on the cardiovascular system, such as seen in HIV-infections. The purpose of this article is to show the importance of immune pathogenesis in different diseases of heart and vessels in childhood, seen with the eyes of a pediatric cardiologist. The focus will lie on novel immune findings relating to rhythm disturbances (especially congenital heart block), rheumatic heart disease, autoimmune myocarditis and cardiac failure and vasculitis (especially Kawasaki disease). In addition some data on arteriosclerosis will be discussed. This is obvious no disease state in children, but prevention might start in childhood, as the pathophysiologic mechanisms are progressively disentangled. This field of "immune cardiology" is still very chaotic, and practical consequences are still unconsolidated at this moment, but they are likely to come and change our therapeutic approaches. The references may guide the pediatrician in her or his further readings.

Descriptors: IMMUNOLOGY, PATHOGENESIS, CARDIOVASCULAR SYSTEM, CARDIOLOGY, PEDIATRICS

It is common knowledge that immune mechanisms are playing a major role in the cardiovascular involvement in rheumatic fever and rheumatic heart disease, systemic lupus erythematosus (SLE) and juvenile rheumatoid arthritis. Both humoral and cellular immune responses are implicated. More recently similar mechanisms are been identified in different forms of vasculitis (polyarteritis nodosa and Kawasaki disease). Over the last years the determinants of the targeting of vessels and heart by (auto) immune mechanisms are explored in greater depth, although the overall picture is still chaotic and diagnostic and therapeutic consequences out of the abundance of basic research are not yet well defined. This article will focus on the immune

mechanisms in the pathogenesis and pathophysiology on the different components of the cardiovascular system.

The pericardium

In literature publications on immune mechanisms of pericarditis are rare. This stays in contrast with its clinical relevance. Every pediatric cardiologist has been puzzled by the post-pericardiotomy syndrome. Treatment with salicylates or steroids in refractory cases is clinical routine, and points to (not fully explored) immune pathogenesis (1). In juvenile rheumatoid arthritis and occasionally in SLE, immune pericardial effusion is noted, but seldom a life threatening complication. Often myocarditis is associated to the clinical picture.

The valves

Rheumatic fever, an immunologic disease triggered by Streptococcal infection can cause severe damage mainly to aortic and mitral valves. Rheumatic heart disease is clearly determined by poverty,

overcrowding, malnutrition and shortage of health-care resources (2). Immune mechanisms relate mainly to T-cell function and to HLA class II antigens (3).

The myocardium

Targeting of the heart by immune processes is a major determinant in myocarditis and dilated cardiomyopathy in the young. The entity "autoimmune heart failure" has been proposed (4). Because viral genetic material and proteins are found in the myocardium of patients with dilated cardiomyopathy, anti-viral and anti-inflammatory therapies are advocated in its prevention or treatment (5). Pediatricians probably were right to include anti-inflammatory and immune-depressing medication in their therapeutic approach to cardiomyopathy (6).

The conduction system

The immune system plays an important role in the pathogenesis of cardiac rhythm and conduction disorders (7). The best explored example is congenital

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heart block in fetus born from mothers with anti-Ro/SS-A (Sjögren syndrome - type A), and anti-La/SS-B antibodies. Congenital heart block has always been a puzzling disease. Only a small number of fetuses will finally develop the disease in the presence of antibodies. The HLA system is thought to be implicated in the pathophysiology (HLA-B27, HLA-DR3). The cross-reactivity of laminin with anti-La antibodies could also be important in the initiation of the autoimmune process. Because the presence of antibodies is not a sufficient reason to develop congenital total block, genetic risk factors inherent to the fetus and the in utero environment probably participate in the pathogenesis (8). Given the uncertainty of all interfering factors and of the value of the markers, the only way of early detection of the disease in the fetus is serial Echo-Doppler fetal examination in all mothers with anti-RO/SS-Antibodies. A rather small therapeutic window could exist for treatment with steroids.

The vessels, mainly the arteries

Peripheral arthritis such as seen in polyarteritis nodosa and Takayasu disease are very rare diagnosis in childhood. The arthritis involving the coronary arteries in Kawasaki disease however has been a major pediatric concern. The immunopathogenesis of vasculitis has been studied intensively over the last years (9). This research identified some important players, but did by far not lead us yet to a full understanding of the process (10). Although arteriosclerosis, also a form of vasculitis, is not seen in childhood, it is worth to make a little sidewalk towards this disease. Innate and adaptive immunity have been shown to play an important role in its pathogenesis (11). Hansson et al. state that "few human diseases have a longer incubation period than atherosclerosis". The individual susceptibility to this lethal disease could originate from the way the child's immune system is built and challenged. In this line of thinking, we just mention the possible role of "natural antibodies" produced by B1 cells. Some of these antibodies recognize microbial components such as phosphorylcholine of pneumococci, but also the oxidized phospholipids of

low-density lipoprotein. Maybe, the only period we can structurally influence arteriosclerosis is child's age.

Are there diagnostic and therapeutic consequences?

The list of possible determinants and markers of the immune process gets longer every year, but the meaning and timing of these markers are still debatable. This should however not discourage the pediatric cardiologist. Knowing that immune mechanisms are important is already an important clue to therapy. We might expect therapeutic advances earlier than diagnostic ones. The treatment of Kawasaki disease is a good example how we made progress just by knowing that immune mechanisms are important. Since gamma-globulins are given early in the course of the disease the frequency of coronary aneurisms has declined drastically (12). Refractory Kawasaki has been described to respond to Tissue Nuclear Factor or TNF-alpha-blockers such as Infliximab (13). The mechanisms of action neither of gamma-globulins or TNF blockers are really known, but isn't this true for many treatments.

CONCLUSION

The cardiovascular system is clearly targeted by immune pathogenic mechanisms. The determinants and possible markers are a booming field of research. This research will change drastically our understanding and treatment of many heart diseases.

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Sažetak

KOLIKO JE IMUNOSAN KARDIOVASKULARNI SUSTAV? STAJALIŠTE PEDIJATRIJSKOG KARDIOLOGA

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Kod sve većeg broja bolesti srca i krvnih žila djece uočavaju se imunološki mehanizmi. Sve strukture srca i krvnih žila mogu biti pogođene imunološkom reakcijom. Ovaj pregled neće se baviti imunodeficijencijama i njihovim posljedicama na kardiovaskularni sustav, kao što je to slučaj kod HIV-infekcija. Svrha ovog članka je pokazati važnost imunološke patogeneze u različitim bolestima srca i krvnih žila djece, sa stajališta pedijatra kardiologa. Pozornost će biti usmjerena na nove imunološke nalaze povezane s aritmijama (posebno kongenitalni srčani blok), reumatskim bolestima srca, autoimunim miokarditisom i srčanim zatajenjem te vaskulitisom (Mb. Kawasaki). Podaci o arteriosklerozi su također predstavljeni. Očito je, da ovo nije bolest djece, ali prevencija bi mogla početi u dječjoj dobi, pošto se patofiziološki mehanizmi ubrzano razumijevaju. Područje "imunološke kardiologije" je još uvijek veoma kaotično, i iako je praktična primjena još uvijek nedorečena, vjerojatno će utjecati na terapijski pristup.

Deskriptori: IMUNOLOGIJA, PATOGENEZA, KARDIOVASKULARNI SUSTAV, KARDIOLOGIJA, PEDIJARIJA