Review article

The Heart in Systemic Autoimmune Disorders

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Introduction

The heart and the vascular system are frequent and characteristic targets of several systemic autoimmune diseases[1]. The connective tissue diseases, which include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), ankylosing spondylitis (AKS), scleroderma, polymyositis and dermatomyositis, and mixed connective tissue disease (MCTD), are the systemic illnesses that most commonly affect the heart. Although these autoimmune-mediated inflammatory diseases predominantly affect the musculoskeletal system, the associated heart disease is an important cause of morbidity and mortality. The reported prevalence rates of heart disease in these conditions vary widely because of differences in patient characteristics, preselection bias, variability in the definition of cardiovascular abnormalities, and differences in the diagnostic methods used[2]. A second group of autoimmune disorders that can affect the heart are the vasculitis syndromes, some of which are rare in childhood and all of which are still poorly understood in terms of pathogenesis[3]. In this review we will describe the cardiac manifestations of the more common of these disorders in children.

I. Autoimmune Connective Tissue Diseases
Systemic Lupus Erythematosus (SLE)

SLE is an autoimmune multisystem disorder of unknown etiology[4], affecting between 1 and 6 in 100,000 children[5]. In 20% of cases, the onset of SLE is seen before 16 years of age[6]. The diagnosis of SLE is made when 4 out of the 11 criteria, defined by the American Rheumatology Association, are met[4]. SLE has an overall mortality of more than 20% at 10 years. Heart disease is one of the most common causes of death of SLE patients[2].

Pericardial involvement is the most frequent cardiac affection in SLE [7], occurring at some point in over half of the patients with active SLE [8]. In most of these patients, the pericardial involvement is clinically silent and benign in course. Pericardial tamponade can occur, and the differential diagnosis should then include infection and uremia [9].

The prevalence of ***valvular disease*** in SLE in post-mortem studies has ranged from 13% to 100% [2].Its pathogenesis is believed to be due to immune complex deposition and complement activation, leading to an acute, chronic, or recurrent inflammation of the valve leaflets. The presence in the leaflets of immune complexes, complement, antinuclear antibodies, lupus erythematosus cells, and hematoxylin bodies support this theory [10]. Transesophageal echocardiography is more sensitive in detecting valvular lesions in SLE than transthoracic echocardiography. ***Valvular regurgitation,*** usually mild, is the most common valvular affection occurring in up to 79%. The mitral valve is most commonly affected, followed by the tricuspid, aortic and pulmonary valves. ***Libman-Sacks endocarditis*** is almost exclusively seen on the mitral and aortic valves. The masses are usually less than 1 cm^2 in size with irregular borders and heterogenous echodensity but no independent motion. They can be located on any portion of the valve, on the atrial surface of the mitral valve, and the arterial surface of the aortic valve. ***Abnormal valve thickening*** also affects the left sided valves and is usually generalized, although it can predominate on the mid and tip portions. It is commonly associated with valvular regurgitation, valve masses or both. ***Valve stenosis*** and involvement of the annular or subvalvular apparatus are rare[2]. A unique feature of SLE is that valvular abnormalities frequently resolve (24%), appear de novo (12%), or persist but change over time (40%). The mortality at 5 years in patients with SLE and heart disease is about 20% and is predominantly related to valvular disease[11]. Infective endocarditis can be the initial presentation of valvular disease in some patients. Flares of SLE requiring high- dose steroids and cytotoxics frequently precede or accompany infection. Patients with SLE should probably receive antibiotic prophylaxis against infective endocarditis prior to any dental or nonsterile procedures. Additionally, prophylactic antiplatelet therapy should be considered in patients with SLE as valvular lesions can serve as a substrate for cardioembolism[2].

Pulmonary hypertension may occur in patients with SLE, and may precede its onset by several years[12]. Pulmonary hypertension in SLE may be due to pneumonitis, vasculitis, thromboembolism, or thrombosis in situ. Frank vasculitis is quite rare, or the lesions may be identical to those with

idiopathic pulmonary hypertension[13]. ***Myocarditis*** can occur in patients with SLE, and can progress to arrhythmias and heart failure[7]. The association between T cell proliferation and myocarditis in patients with SLE suggests a role for a cellular mechanism in its pathogenesis[14]. ***Accelerated atherosclerosis*** is a recognized feature of SLE, reflecting a high prevalence of conventional risk factors, long-term corticosteroid use, and the presence of antiphospholipid antibodies. Additionally, mechanisms directly related to SLE may stimulate premature vascular disease in view of the fundamental role of inflammation in atherogenesis and recent epidemiologic observations associating markers of inflammation with prevalent atherosclerosis and incident cardiovascular disease. Roman et al[15] noted a striking increase in the presence of underlying atherosclerotic and myocardial disease in the setting of SLE compared with a studied control population that was not dependent on an excess of conventional risk factors for atherosclerosis and LV hypertrophy. A rare cardiovascular manifestation of SLE, reported in only 15 cases, is ***aortic dissection***. These patients were all young, had systemic disease; were mostly hypertensive, and had received corticosteroids for a relatively long period of time[16].

Neonatal Lupus Erythematosus (NLE)

NLE is a model of passively acquired autoimmune disease where pathogenic antibodies are transplacentally acquired by the fetus[17]. Mothers may have SLE, Sjörgen syndrome, or other connective tissue disease, or may be completely healthy at the time of delivery[18]. Cimaz et al[19] reported that the presence of anti Ro with or without anti-La autoantibodies, rather than the type of maternal autoimmune disease, is a risk factor for the development of NLE. The most important, irreversible and severe clinical manifestation of NLE is ***congenital complete heart block (CCHB)*** which occured in 1.6% of prospectively studied pregnancies of mothers with positive anti-Ro and/or anti-La autoantibodies, and caries a significant risk of morbidity and mortality. Other cardiac features of NLE include ***congenital malformations and less severe conduction abnormalities***, notably prolonged QT interval[19]. Monitoring for fetal bradycardia due to CCHB during high risk pregnancies is recommended by weekly fetal echocardiograms between 18 and 24 weeks gestation. Prenatal therapy with steroids and plasmapheresis has yielded mixed results. Postnatal therapy involves cardiac pacing in two-thirds of surviving infants[4].

Juvenile Rheumatoid Arthritis (JRA)

JRA is the most common rheumatic disorder of childhood and is classified into pauciarticular, polyarticular and systemic forms[20]. It is also further subdivided into rheumatoid factor positive or negative[21]. Clinical evidence of cardiac involvement in JRA is uncommon[22]. A diffuse, non specific ***fibrinous pericarditis*** occurs in 50% of patients with RA but is clinically silent, although sizeable effusions can occur[22]. Chronic symptomatic pericarditis can also occur and may require steroid therapy[23]. ***Valvular disease*** associated with RA is usually subclinical, and includes valvular thickening, valvular granulomas, and valvular regurgitation. Its incidence is variable but is more common in patients with erosive polyarticular and nodular disease, systemic vasculitis and high serum titers of rheumatoid factor. Valvular granulomas are unique to the disease, and resemble rheumatoid nodules. They are more commonly seen on the basal portions of the leaflets, are single, and the surrounding leaflet has an unremarkable appearance and mobility. Data suggest no association of valvular disease with age, duration of RA, or peripheral nodular disease[2, 24]. ***Pulmonary hypertension*** has been described in RA, most commonly due to interstitial fibrosis with medial thickening and intimal proliferation. Small and medium-sized PA vasculitis is rare but may occur in the absence of significant parenchymal lung disease and portends a grave prognosis[13]. Cardiovascular mortality accounts for almost half the deaths in RA, mainly due to ***ischemic heart disease (IHD)***[25]. Studies in RA have indicated accelerated carotid atherosclerosis[26]. In RA, the primary site of inflammation is the synovial tissue from which cytokines can be released into the systemic circulation. These circulating cytokines can alter the function of distant tissues and generate a spectrum of proatherogenic changes that include insulin resistance, a characteristic dyslipidemia, prothrombotic effects, pro-oxidative stress, and endothelial dysfunction. Premature mortality in RA, largely due to cardiovascular disease, is related to the number of inflamed joints[27].

Juvenile Dermatomyositis/Polymyositis/Mixed Connective Tissue Disease (MCTD)

Although Juvenile dermatomyositis is the most common myopathy of childhood, it affects only 3 children per million per year[28] between the ages of 4 and 10 years[4]. ***Myocarditis and pericarditis*** are the most common forms of heart disease associated with this group of disorders. ***Coronary artery disease, conduction disturbances, valvular disease and pulmonary hypertension*** are uncommon[2].

Mitral valve prolapse can be found in up to 50% of patients but no other specific valvular disease has been reported[29]. The myocardium in dermatomyositis may show loss of striations, fragmentation, and vascularization of muscle fibres with interstitial swelling and edema[30]. Although pulmonary hypertension is rare, when it does occur, it appears to be associated with a high mortality[31].

Scleroderma

Scleroderma is a multisystem disease of unknown etiology that extends from a benign localized scleroderma to severe progressive systemic sclerosis, which can be fatal. Childhood scleroderma is rare with linear scleroderma being the common form in childhood[4]. Clinically overt heart disease occurs in 25% of patients and includes *coronary artery disease, myocarditis, pericarditis, pulmonary and systemic hypertension*, and less commonly, *valvular heart disease, arrhythmias, and conduction abnormalities*. Heart disease is the third major cause of death in these patients due to ischemic heart disease, heart failure, sudden death and pericarditis[2]. In *primary systemic sclerosis of the heart*, a myocardial fibrosis occurs that bears no direct relation to large or small vessel occlusion or any other anatomic abnormality, and tends to be patchy, involving all levels of the myocardium[32]. The morphologic characteristics of the myocardial lesions of primary cardiac systemic sclerosis are consistent with a Raynaud's phenomenon of the heart[33]. The prevalence of *pulmonary arterial hypertension (PAH)* has been reported to be higher among patients with limited cutaneous sclerosis than among those with diffuse systemic sclerosis[34]. Antiendothelial cell antibodies (AECA) may be an important marker for disease severity in scleroderma, with one study demonstrating that the incidence of PAH was higher in patients with AECA than in those without the antibody[35]. *Pericardial disease* in systemic sclerosis is usually clinically silent and benign, with an incidence of 40% as detected by echocardiography, especially in patients with diffuse disease. Large effusions, however, may carry a grave prognosis. Histology of the pericardium has been characterized by leukocytoclastic vasculitis[34].

Ankylosing Spondylitis (AKS)

AKS, an HLA-B27 related autoimmune disease, is characterized by inflammation of the vertebral and sacroiliac joints, peripheral arthritis and anterior uveitis. AKS affects the heart predominantly in the form of *valvular* and *aortic root disease* and *conduction disturbances* with a prevalence of less than 10%. The valvular disease can precede other clinical manifestations of AKS. The valvular and aortic root disease associated with AKS results in cusp thickening and retraction, thickening of the aorto-mitral junction (subaortic bump), proximal aortitis resulting in aortic root thickening and dilation and aortic and mitral regurgitation. Complicating infective endocarditis can occur in patients with no known or subclinical disease, and both prophylactic antibiotic therapy for infective endocarditis and prophylactic antithrombotic therapy should be considered in these patients[2].

II. Vasculitis Syndromes

Primary vasculitis is rare in children with an overall estimated annual incidence among children under 17 years of age of 20.4/100 000[36].

Kawasaki Disease (KD)

Although KD is classified as a vasculitis, unlike other inflammatory conditions of blood vessels, it is a self-limited condition, with fever and manifestations of acute inflammation lasting for an average of 12 days without therapy[37]. It is diagnosed by clinical criteria (Table 1)[38], not histology or angiography. It is almost entirely a disease of children, with 80% to 90% of cases occurring before the fifth birthday. Death can occur in up to 1.5% of untreated children. Many aspects of KD suggest that it is caused by a transmissible agent[3].

The cardiovascular involvement in Kawasaki disease can be extensive. Kato *et al*,[39] reported a review of 1438 cases and found *transient coronary artery dilatation* in 28%, *coronary artery aneurysm* (Figure 1 and 2) in 18%, and other arterial aneurysms in 2%. Other cardiac involvement included *myocarditis* in > 50%, *pericarditis/effusion* in 18%, *myocardial infarction* in 1.4%, *mitral regurgitation* in 0.9%, and *aortic regurgitation* in 0.2%. Risk factors for the development of coronary artery aneurysm include prolonged or recurrent fever, white males, age less than one year, elevated white blood cell count and CRP level, and increased levels of cytokines including interleukin, TNF, and elevated beta thromboglobulin, an indicator of increased platelet activation[40, 41].

**Table 1.** Criteria for the diagnosis of Kawasaki disease (KD)[3].

Fever lasting 5 days or more (4 days if treatment with IVIG eradicates fever) plus at least four of the following clinical signs not explained by another disease process (numbers in parentheses indicate the approximate percentage of children with KD who display the criterion):
1. Bilateral conjunctival injection (80-90%)
2. Changes in the oropharyngeal mucous membranes (including one or more of the following symptoms: injected or fissured lips, strawberry tongue, injected pharynx) (80-90%)
3. Changes in the peripheral extremities, including erythema or edema of the hands and feet (acute phase) or periungal desquamation (convalescent phase) (80%)
4. Polymorphous rash, primarily truncal; nonvesicular (90%)
5. Cervical lymphadenopathy: anterior cervical lymph node at least 1.5cm in diameter (50%)

IVIG: intravenous immunoglobulin; KD: Kawasaki disease
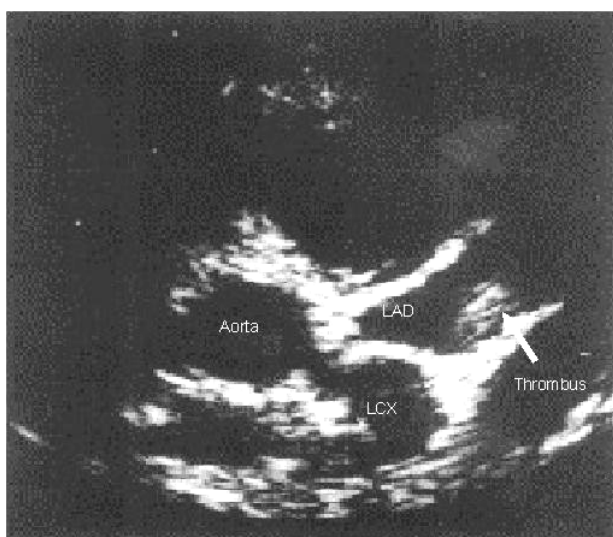
Figure 1. Dilated left anterior descending and left circumflex coronary arteries with aneurysm formation and a thrombus in the left anterior descending coronary artery seen on transthoracic echocardiography (short axis parasternal view). Courtesy of Prof. Maiy H. Elsayed, Professor of Cardiology, Faculty of Medicine, Ain Shams University, Egypt.
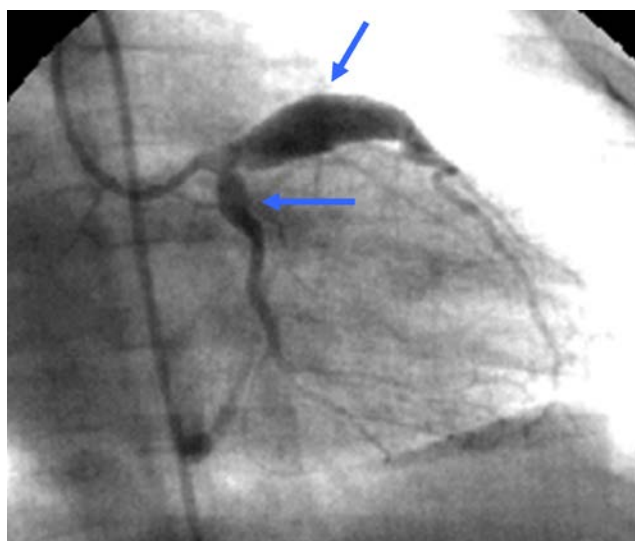
Figure 2. Selective coronary angiography showing saccular aneurysms of the branches of the left coronary artery. Courtesy of Prof. Maiy H. Elsayed, Professor of Cardiology, Faculty of Medicine, Ain Shams University, Egypt.

Table 2: Treatment of acute Kawasaki disease (KD) [53]
Intravenous gamma globulin (IVGG)
- 2g/kg as single infusion over 12 hours; should be given within 10 days of onset of fever
Acetylsalicylic acid (ASA)
- 80-100 mg/kg, divided into 4 doses, until patient is afebrile, then 3-5 mg/kg every day for 6-8 weeks*
Evidence based guidelines do not exist for the management of patient sin the following situations:
- Patients who are afebrile at the time of the presentation:
  - IVGG usually not recommended; give low dose ASA
- Patients with persistent or recurrent fever after the initial dose of IVGG
  - May repeat IVGG dose or give intravenous corticosteroid therapy
- Patients with evidence of myocarditis (i.e. diminished ventricular function; ventricular arrhythmia)
  - Supportive therapy, may give intravenous corticosteroid therapy or repeat IVGG

* If varicella or influenza develops, ASA therapy should be stopped to reduce the risk of
Reye's syndrome. Discontinue ASA therapy 6-8 weeks after onset of illness if no coronary artery aneurysms are observed on follow up echocardiography

IVGG: intravenous gamma globulin; ASA Acetyl Salicylic Acid

Kato, et al[42] followed a cohort of 594 consecutive children for 10–21 years. Coronary aneurysms were present in 25%. Patients with normal findings at the first study did not develop future cardiac findings. Coronary aneurysms showed regression in 55%, but by 10–21 years later, 28 had stenosis within the coronary aneurysm, with myocardial infarction occurring in 11, 5 of whom died. Stenosis developed in 12 of the 26 patients with giant aneurysms and no regression occurred. Systemic artery aneurysms developed in 13 patients (2%), and valvular disease appeared in 7 (1.2%). The pathologic mechanisms of regression of aneurysms include marked thickening of the intima, which is rich in smooth muscle cells, in vessels that resume a calibre similar to normal vessels If massive thrombosis occurred, there is more calcification, fissuring, deposition of protein like material, and hyaline degeneration, similar to athero-sclerosis[43,44,45].

The wall motion abnormalities associated with ischemia during the early phases of KD can show significant improvement with time because of canalization and development of collateral vessels. Collateral vessel development is significantly correlated with a younger age at onset of KD, especially in patients with segmental rather than localized stenoses[46].

Cellular infiltration and edema in the myocardium are found frequently in postmortem examination of patients who died within 30 days from onset of KD [47]. Tissue from myocardial biopsies performed one month to 11 years after onset showed varying degrees of cellular infiltration, fibrosis, and abnormal myocyte structure[48]. The severity of *myocarditis* is not necessarily linked with the presence of coronary artery dilatation and IVIG has been shown to improve function[49]. Mild *valvulitis* assessed by mild regurgitation by Doppler echocardiography is very frequent in the acute phase, but severe valvulitis leading to persistent significant regurgitation is rare (~ 1 %). Severe valvulitis can occur in patients with mildly dilated or normal appearing coronary arteries or may be due to ischemic papillary muscle dysfunction[50]. *Aneurysms of the aorta and non-coronary medium size muscular arteries* have been reported and need serial evaluation[51]. *Arrhythmias*, both tachy- and bradyarrhythmias, can occur during the acute phase of KD. Late ventricular arrhythmia is usually associated with significant coronary occlusion[52]. The treatment of KD is outlined in Table 2.

Polyarteritis Nodosa (PAN)

PAN is a systemic necrotizing vasculitis with aneurysm formation affecting medium or small arteries[3]. Pediatric PAN is quite rare and when it does occur before adulthood, PAN incidence peaks at 9 to 10 years of age, and may be slightly more common in boys than in girls[54]. Systemic PAN may involve virtually any muscular artery. Consequently, in addition to constitutional symptoms, it may cause a vast array of organ dysfunction. *Coronary arteritis* may be seen at presentation or during the course of the disease[55]. Treatment usually aims at decreasing systemic vascular inflammation, mainly with high-dose steroid and other immunosuppressive agents. Recent reviews of PAN in children suggest an excellent overall prognosis, with a 4-year mortality rate under 5%[54].

Takayasu arteritis (TA)

TA is the third most common form of childhood vasculitis[56]. The cause of TA remains unknown, although a primarily T-cell–mediated mechanism is suggested[57]. TA lesions consist of granulomatous changes progressing from the vascular adventitia to the media[58] and its diagnosis is based on the distribution of involvement—primarily the aorta and its branches—and the young age of patients, typically below 40 years[59]. Onset of TA is most commonly during the third decade of life, but childhood disease has been reported as early as the first year of life[60]. In a recent review of childhood TA, the mean age of onset was 11.4 years, and two thirds of the patients were female[61]. Signs and symptoms included hypertension, cardiomegaly, elevated ESR, fever, fatigue, palpitations, vomiting, nodules, abdominal pain, arthralgia, claudication, weight loss, and chest pain. Angiography has been the standard method used for diagnosis. as the size of the vessels involved and the spotty nature of the vascular inflammation make biopsies impractical. In recent years, CT and MR angiograms have proven to be as useful and far less invasive, with MRI having the added advantage of revealing evidence of ongoing vessel wall inflammation. This information is particularly helpful because of the need to suppress the vasculitis completely to prevent disease progression, and because laboratory markers may be entirely normal despite ongoing inflammation[62]. Steroids and immunosuppressive agents used in other vasculitides have shown variable efficacy in TA. A recent report in adults documented a high response rate to TNF-inhibitors[63]. Before starting such treatment, however, it is important to test patients for

tuberculosis, because aortitis is associated with mycobacterial infections[64].

III. Rheumatic Fever (RF)

RF is the most frequent rheumatic disease and the main cause of acquired cardiac disease during childhood and adolescence in developing countries[65]. A sizeable body of evidence supports the role for the group A β-hemolytic streptococcus in the etiology of RF. There have been several hypothesis to explain a streptococcal pathogenesis for RF, the most feasible being the concept of antigenic mimicry in association with an abnormal immune response. A role of human host genetic or acquired variability in susceptibility to RF has also been demonstrated[66] but studies of HLA and the B-lymphocyte antigen D8/17 have not yielded results that can be utilized to identify susceptible individuals[67]. RF occurs mainly between the ages of 5 and 15 years, but can occur in children who are younger than 5 years[68]. Recent data suggests that almost 90% of those who get RF develop rheumatic heart disease (RHD)[67]. Cardiac involvement, the only manifestation capable of causing death or leaving long-term sequelae, usually presents as a *pancarditis* and appears during the first three weeks after the onset of the disease. The patient complains of fatigue, anorexia, and may present with chest pain and dyspnea. *Myocarditis* is common and may evolve into congestive heart failure. It is usually associated with *valvulitis*. The mitral valves are most often affected, and the simultaneous involvement of mitral and aortic valves is also common. Isolated *pericarditis* in RF is rare and suggests a different diagnosis, such as JRA or SLE[65]. Primary prevention aims at identifying and treating streptococcal sore throat, while secondary prevention aims at preventing further attacks of RF by preventing the occurrence of streptococcal sore throat. Both have proved difficult to implement at a community level, and some authors believe that primary prevention will only be feasible if an antistreptococcal vaccine becomes available[67].

Summary

Cardiac disease is a recognized and important consequence of most autoimmune diseases of childhood. Its prevalence and severity is variable among the different disorders, and among patients suffering from the same disease. The factors influencing the development of heart disease in these are still not fully understood, but it is a major cause of morbidity and mortality in all of them. Early recognition of cardiac affection in children suffering from autoimmune disorders may improve patient outcome and further research is warranted into the underlying causes and modes of prevention and treatment.

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