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ACQUIRED AND GENETICALLY PREDISPOSED HEART DISEASE IN CHILDREN

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Abstract

Types of acquired heart disease among children include: cardiomyopathy, endocarditis, myocarditis, pericarditis, Kawasaki disease, arrhythmia, hypertension, rheumatic fever, and obesity. These are diseases that occur after birth, as opposed to congenital heart disease, which is present at birth. Acquired heart disease in children constitutes diagnoses which do not occur in adults (eg. Kawasaki disease), or which may be similar to conditions present in adolescents and adult patients (eg. dilated cardiomyopathy). Most frequently diagnosed are rheumatic fever and Kawasaki disease. Children who are diagnosed and treated for congenital heart disease are at higher risk of developing endocarditis and cardiomyopathy. Although heart disease in childhood has a complex aetiology – and is often caused by unknown factors – a wide palette of diagnostic tests is required to determine its cause, including: genetic, echocardiography, X-ray, MRI, CT, heart catheterisation, endomyocardial biopsy, and nuclear studies. Pathological process directly affects cardiac structures, causing myocardial dysfunction. If myocardial function is suspected, it is necessary to take a detailed history of the disease, along with a physical examination, and apply a diagnostic and therapeutic algorithm in order to stabilise a haemodynamically compromised patient with acquired heart disease.

Key words: acquired, heart disease, children

Introduction

Types of acquired heart disease in children include: cardiomyopathy, endocarditis, myocarditis, pericarditis, Kawasaki disease, abnormal heart rhythm, hypertension, rheumatic fever, and obesity. Some of these conditions will be reviewed in this paper, according to current references.

Cardiomyopathy

Cardiomyopathy is defined as a primary myocardial disease of the heart muscle itself, not associated with congenital, valvular, or coronary heart disease or systemic disorders.

Prevalence is 10/100000 in the neonatal period, 36/100000 for all age groups (Dilated Cardiomyopathy), and 2/100000 for all age groups (Hypertrophic Cardiomyopathy).

In this condition, pathological processes directly affect the heart's structure, causing myocardial dysfunction. It is the third most common heart disease in the USA, and the second most common cause of sudden death in adolescence.

According to **WHO classification**:

Idiopathic (Primary):

- dilated cardiomyopathy
- hypertrophic cardiomyopathy
- restrictive cardiomyopathy
- arrhythmogenic right ventricular cardiomyopathy
- specific cardiomyopathy
- non-classified cardiomyopathies which include fibroelastosis and amyloidosis hypertension

Specific (Secondary):

- infective, metabolic, toxic, immune-cause, systemic disease, hereditary cause

Functional classification

Dilated (congestive, DCM, IDC) cardiomyopathy

- ventricular dilatation with decreased contractile function

Hypertrophic cardiomyopathy (IHSS, HCM, HOCM)

- massive ventricular hypertrophy with increased contractile function, ventricular filling is impaired by relaxation abnormalities

Restrictive (infiltrative) cardiomyopathy

- restriction of diastolic filling of the ventricles

Contractile function of the ventricle may be normal, but there is marked dilatation of both atria.

Dilated or Congestive Cardiomyopathy

- the most common cause of dilated cardiomyopathy is idiopathic (80%)
- dilatation of the left ventricle and weakening of systolic contraction, decreasing cardiac output.

Myocarditis is a myocardial inflammation, in the absence of acute or chronic ischaemia. Dilated cardiomyopathy is the result of primary myocardial damage and activation of the immune system, in 30-40% persons with a predisposition.



Histologic and genetic examinations from endomyocardial biopsies are one option for the distinction of acute myocardial damage from idiopathic cardiomyopathy developing from a genetic predisposition.

Clinical-pathological classification

- fulminant myocarditis:
- acute myocarditis
- chronic active myocarditis
- chronic persistent myocarditis

Incidence: 3-10/100000; 20000 new cases per annum in the USA.

Deaths caused by progressive heart failure, systemic or pulmonary embolisation, and arrhythmia: over the course of 1 year, 25%; two years, 35-40%; and 5 years, 40-80%.

Stabilisation occurs in 20-50% cases, but complete recovery is very rare.

Causes of myocarditis

<i>Infective</i>			<i>Noninfective</i>
Virus	Bacterial	Fungi	Arsen
Influenza A, B	Staphylococcus sp.	Aspergillus sp.	Anthacyclines
Adenovirus	Streptococcus sp.	Candida sp.	CO
Coxsackie B	Mycoplasma pneum.	Hystoplasma sp.	Ethanol
Epstein Barr	Treponema pallidum	Blastomycosis	Fe
CMV, ECHO	Mycobacteriae	Protozoa	IL 2
Hepatitis C	Clostridium sp.	Toxoplasmosis	Cocaine
HIV	Neisseria gonorrhoea	Malaria	
Parvovirus, HSV		Larva migrans	

<i>Hypersensitivity</i>	<i>Systemic disease</i>
Antibiotics	Collagen-vascular disease
Diuretics	BID
Antiepileptics	Giant cell myocarditis
Digoxin	Thyrotoxicosis
Lithium	
Dobutamin	

Pathogenesis

Animal research in viral myocarditis points to three important mechanisms:

1. Direct myocardial affection
2. Local and systemic immunological activation

3. Cellular and humoral activation (activation of cellular CD4 and humoral B cell proliferation) response, leading to progression of local inflammation, production of antibodies against myocardium and, consequently, mionecrosis

Clinical manifestation

- it can have a wide spectrum of presentation, and can imitate numerous noncardial diseases;
- clinical aspects vary from asymptomatic changes in ECG, to cardiogenic shock.

Key symptoms are: virus syndrome, autoimmune or infective disease, and adverse effects of medicaments or toxins (rarely). Additional signs are: chest pain, dyspnoea, fatigue, ablation, agitation, peripheral hypoperfusion, hypotension, palpitations, fever, myalgia, respiratory and gastrointestinal symptoms, gallop rhythm, tachycardia, atrial and ventricular arrhythmia, syncope, and lymphadenopathy.

Based on 10 years' retrospective study (from January 2001 to December 2011) in children with proven myocarditis in the Children's Emergency Department of Kananga Kerbeau Hospital, Singapore (Canadian Journal of Emergency Medicine) M score was defined. M scores are obtained by gastrointestinal symptoms, and symptoms of hypoperfusion, hypoxia, respiratory distress, and hepatomegaly.

Investigations: Laboratory analysis of blood, stool, and urine samples; PCR

Specific cardiomarkers are: CK, CKMB ($>22\text{ng/ml}$), troponin ($>0.9\text{ng/ml}$), although when interpreting results of laboratory studies, it is important to note that the troponin level is raised in less than 50% of patients with acute myocarditis; and BNP raised in response to ventricular compliance, which occurs in myocarditis and heart failure (a very high degree of sensitivity can predict the need for a heart pump).

ECG: Sinus tachycardia, microvoltage (QRS amplitude $\leq 5\text{mm}$), LVH, and ST-T changes. Left or right atrial hypertrophy may be present (Fig. 1).

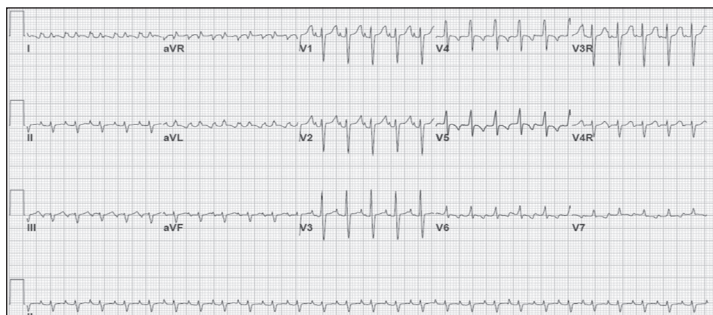


Figure 1. ECG: sinus tachycardia, microvoltage, changes in ST segment and left precordial leads

X-ray: bronchopneumonial focus, generalised cardiomegaly is usually present, with or without signs of pulmonary venous hypertension or pulmonary oedema. (Fig. 2).

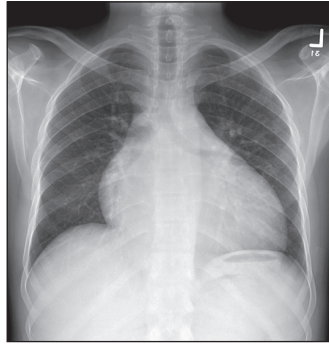


Figure 2. X-ray: situs solitus, mezocardia, cardiomegaly, changes of bronchopulmonal markings

ECHO: LV dysfunction, dilatation of the left heart cavities, poor contractility, pericardial effusion (Fig. 3). Mitral inflow Doppler tracing demonstrates a reduced E velocity and a decreased E/A ratio.

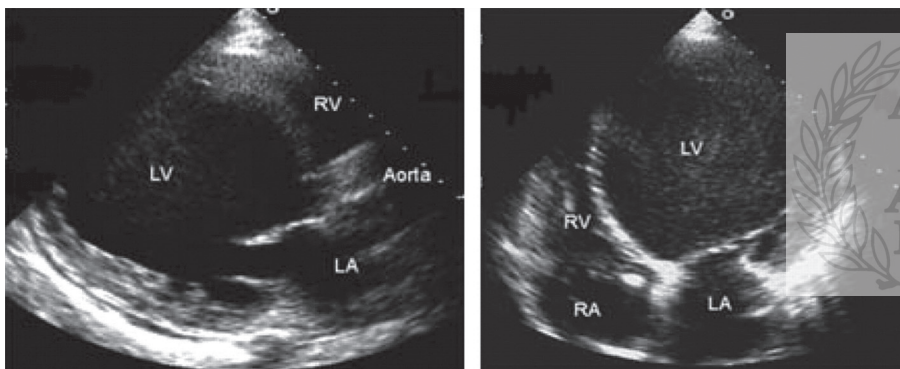


Figure 3. 2D Echocardiography parasternal long axis and 4-chamber view: left ventricular dysfunction, dilatation of left heart chambers, global hypokinesia, decreased mobility of posterior wall

MRI in acute illness accurately demonstrates the oedema of the myocardium.

Endomyocardial biopsy is a criterion for differential diagnosis in a patient with dilated cardiomyopathy. It is performed in circumstances of: unexplainable heart failure within two weeks, with or without LV dilatation; suspected fulminant or giant cell myocarditis; patients who do not respond to therapy within two weeks; and patients with a positive family history. In 1984, the American College of Cardiology Foundation/American Heart Association/European Society of Cardiology (ACCF/AHA/ESC) published its recommendations for classification based on the results of endomyocardial biopsies. Clinical praxes regarding endomyocardial biopsy in acute myocarditis vary widely. Many centres have performed it only rarely, in few patients. Mandatory, if chronic, persistent myocarditis (giant cell) is in question.

Dallas criteria: *active myocarditis, borderline myocarditis, absence of myocarditis*

Criteria for diagnosis are:

1. heart failure, fever, virus syndrome, fatigue, dyspnoea, chest pain, palpitation, syncope
2. laboratory (CKMB, Troponin, BNP), ECG, ECHO (LV dilatation, paradoxal septal movement)
3. MRI heart, endomyocardial biopsy, PCR of viral genome

Management

- Antibiotics (suspected bacterial infection);
- Inotropic support (dobutamine 2.5-15mcg/kg/min, dopamine 5-20 mcg/kg/min) is often needed;
- Digoxin – not in acute phase, and only in stable patients. First 20-30 mcg/kg divided into three doses, then 8-10 mcg/kg divided into two doses. Some centres no longer use digoxin as an inotropic drug in children;
- Diuretics (furosemide 1-2mg/kg/dose, spironolactone 1-3mg/kg/day);
- Control of fluid balance;
- Angiotensin-converting enzyme (ACE) inhibitors (captopril, enalapril) are an integral part of therapy, as is bed rest or restriction of activity;
- Immunoglobulines – data are controversial;
- Critically ill children may require intubation and mechanical ventilation;
- Beta adrenergic blocker therapy in children with chronic heart failure has been shown to improve LV ejection fraction. Carvedilol is a beta-adrenergic blocker with additional vasodilation action;
- Antiplatelet agents (aspirin) should be initiated. The propensity for thrombus formation in patients with dilated cardiac chambers and blood stasis may prompt use of anticoagulation with warfarin. If thrombi are detected, they should be treated aggressively with heparin initially and later switched to long-term warfarin therapy;
- Patients with arrhythmia may be treated with amiodarone or other antiarrhythmic agents;
- Amiodarone is effective and relatively safe in children. For symptomatic bradycardia, a cardiac pacemaker may be necessary. An ICD may be considered, but there is limited experience with this device in children;
- Immunoglobulin;
- Intracardial and intracoronary application of stem cells;
- Supportive treatment: gastro protective, vitamins, high-energy nutrition;
- Heart transplantation.

Doxorubicin cardiomyopathy

Doxorubicin cardiomyopathy is becoming the most common cause of chronic heart failure in children. Its prevalence is nonlinearly dose related, occurring in 2-5% of

patients who have received a cumulative dose of 400 to 500 mg/m², and up to 50% of patients who have received more than 1000 mg/m² of doxorubicin. Risk factors include age (younger than 4 years), and a cumulative dose exceeding 400 to 600 mg/m². A dosing regimen with larger and less frequent doses has been raised as a risk factor but not proved.

Hypertrophic Cardiomyopathy (HCM)

The most characteristic abnormality is a hypertrophied left ventricle (LV), with the ventricular cavity usually small or normal in size, with increased contractility and abnormal relaxation. In about 50% of cases, HCM is inherited as a Mendelian autosomal dominant trait and is caused by mutations in one of 10 genes encoding protein components of the cardiac sarcomere (chromosome 14, 11, 15, 11). Its prevalence is 1/500, with total mortality of 1% (in childhood 4-6%). Although asymmetrical septal hypertrophy, a condition formerly known as idiopathic hypertrophic subaortic stenosis (IHSS) is most common (70%), hypertrophy may be concentric (8-10%) or localised to a small segment of the septum (basal septal part 15-20%, apical or lateral wall less than 2%).

Pathophysiology

- obstruction of the outflow tract
- diastolic dysfunction
- myocardial ischaemia
- mitral regurgitation
- arrhythmia

Physical examination

- a sharp upstroke of the arterial pulse
- a grade 1 to 3/6 ejection systolic murmur is most audible at the middle and lower left sternal borders or at the apex. A soft holosystolic murmur of mitral regurgitation (MR) is often present.

ECG: LVH, ST-T changes, and abnormally deep Q waves (owing to septal hypertrophy) with diminished or absent R waves in the left precordial leads, and arrhythmia.

X ray: Mild left ventricular enlargement with a globular-shaped heart may be present. The pulmonary vascularity is usually normal.

ECHO: concentric hypertrophy, localised segmental hypertrophy and asymmetrical septal hypertrophy

HCM: asymmetrical, wall thickness >15 mm, LA>40 mm, LVEDD<45 mm, diastolic function always abnormal

Athletic heart: concentric and regressive, wall thickness<15 mm, LA<40 mm, LVEDD>45 mm, diastolic function always normal



Restrictive Cardiomyopathy

Ventricular diastolic filling is impaired, resulting from excessively stiff ventricular walls. It may be idiopathic, or it may be associated with a systemic disease such as scleroderma, amyloidosis, sarcoidosis, or an inborn error of metabolism (mucopolysaccharidosis). This condition is characterised by markedly dilated atria and generally normal ventricular dimensions and contractility.

Clinical manifestation: intolerance to exercise; weakness and dyspnoea; chest pain.

Physical examination: jugular venous distention; gallop rhythm; systolic murmur due to AV valve regurgitation.

Chest X-ray shows cardiomegaly, pulmonary venous congestion, and occasional pleural effusion.

ECG usually shows atrial hypertrophy. It may show atrial fibrillation and paroxysms of supraventricular tachycardia.

Right Ventricular Dysplasia

The myocardium of the right ventricle (RV) is partially or totally replaced by fibrous or adipose tissue. Onset occurs in infancy, childhood, or adulthood (but usually before the age of 20), with a history of palpitation, syncopal episodes, or both. Sudden death may be the first sign of the disease. Chest X-rays usually show cardiomegaly, and ECG readings most often show tall P waves in lead II (RAH), decreased RV potentials, T-wave inversion in the right precordial leads, and premature ventricular contractions or ventricular tachycardia of LBBB morphologies.

Diagnostic algorithm

I step:

- X-ray with esophagography
- 24 hour ECG
- radionuclide ventriculography
- heart catheterisation, endomyocardial biopsy, microscopy, imunohystology, immunohistochemistry
- laboratory: ABS, lactate, CK, CKMB, LDH, AST, GGT, carnitine, saelen in serum and urine, CRP, SE, electrophoresis, imuno electrophoresis

II step:

- Laboratory: serology examination for viruses, ANA, C3, C4, complement, CIC, anti IgG antibody (Rose-Waaler, Latex tests), antimioleal antibody (AMLAs-IgG, IgM, IgA), antisrcoleal antibody, T and B lymphocyte activity
- neurological findings (EMG, skeletal muscle biopsy)
- ophthalmological findings (cataract in Kearns-Sayerov syndrome)

III step:

- myocardial perfusion scintigraphy with Ga 67 or marked antimiosin antibody
- PET scan

Therapy

Dilated

- anticongestive treatment (digoxin, diuretics, ACE inhibitor)
- anticoagulants (coumarin, heparin)
- beta blocker
- pacemaker
- ICD
- heart transplantation

Hypertrophic

- mild restriction activity
- beta blocker
- transaortic septal miotomy LV and miectomy (Morrow)
- heart transplantation

Restrictive

- diuretics
- anticoagulants
- antiarrhythmic agent
- ICD
- heart transplantation

Rheumatic Carditis

Clinical manifestation: tachycardia; murmur; cardiomegaly; signs of heart failure; hepatomegaly; peripheral oedema; lung oedema (Fig. 4. Echocardiography); detected flow disturbance; decreased contractility; and pericardial effusion.

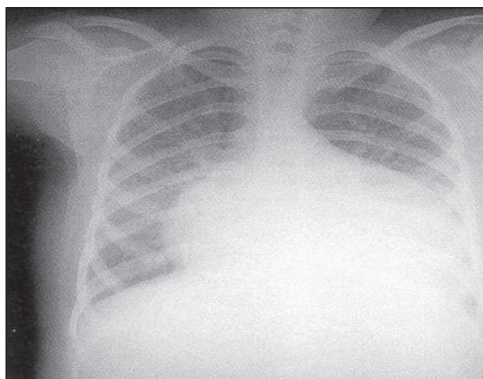


Figure 4. X-ray: situs solitus, cardiomegaly, pericardial effusion in patient with rheumatic fever



Pericarditis

The parietal and visceral surfaces of the pericardium are inflamed. Isolated pericarditis is very rare in a paediatric patient. Possible causes are rheumatic, bacterial, virus or tuberculosis, or complications associated with collagenases or open-heart surgery (postpericardial syndrome). Patients may complain of precordial pain (dull, aching, or stabbing) with occasional radiation to the shoulder and neck. This pain may be relieved by leaning forward and may be worse in a supine position, or with deep inhalation. Pericardial friction rub (a grating, to-and-fro sound in phase with the sounds of the heart) is the cardinal physical sign.

ECG: low-voltage QRS complex caused by pericardial effusion is characteristic but not a constant finding. Secondary to myocardial involvement, the following time-dependent change may occur after an initial ST-segment elevation: return of the ST segment to the baseline with inversion of T waves (2 to 4 weeks after onset [Fig. 5]). *Echo* is the most useful tool in establishing the diagnosis of pericardial effusion, which appears as an echo-free space between the epicardium (visceral pericardium) and the parietal pericardium. Pericardial effusion first appears posteriorly in the dependent portion of the pericardial sac. (Fig. 6.) The presence of a small amount of effusion posteriorly without anterior effusion suggests a small pericardial effusion. A small amount of fluid, which appears only in systole, is normal. With a larger effusion, the fluid also appears anteriorly. The larger the echo-free space, the larger the pericardial effusion. With very large effusions, the swinging motion of the heart may be visualised.

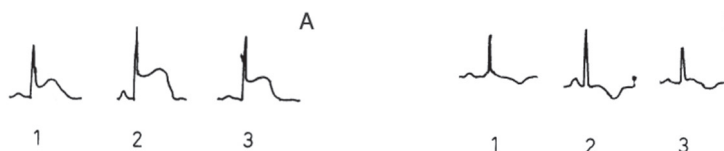


Figure 5. ECG in pericarditis, (A) acute phase, (B) subacute, ST-segment elevation in acute phase in all standard leads

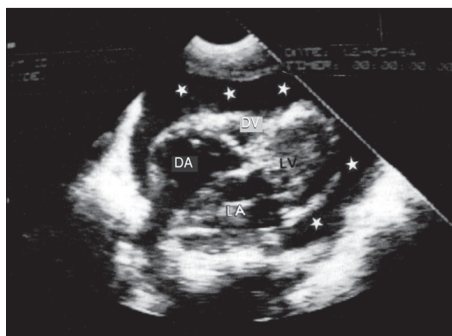


Figure 6. 2D echocardiogram, subcostal 4-chamber view, pericardial effusion (asterix)

Management: For cardiac tamponade, urgent decompression by surgical drainage or pericardiocentesis is indicated. When purulent pericarditis is suspected, urgent surgical drainage of the pericardium is needed. This must be followed by IV antibiotic therapy for 4 to 6 weeks. There is no specific treatment for viral pericarditis. Although rare in children, constrictive pericarditis may be associated with: an early viral pericarditis; tuberculosis; incomplete drainage of purulent pericarditis; hemo-pericardium; mediastinal irradiation; neoplastic infiltration; or connective tissue disorders. In this condition, a fibrotic, thickened, and adherent pericardium restricts diastolic filling of the heart. The treatment for constrictive pericarditis is a complete resection of the pericardium. Symptomatic improvement occurs in 75% of patients.

Endocardial Fibroelastosis

Primary endocardial fibroelastosis is a form of dilated cardiomyopathy with unknown cause, seen in infants and associated with prenatal viral endocarditis. The condition is characterised by diffuse changes in the endocardium with a white, opaque, glistening appearance. The heart chambers, primarily the left atrium and LV, are notably dilated and hypertrophied. Symptoms and signs of heart failure (feeding difficulties, tachypnea, sweating, irritability, pallor, failure to thrive) develop in the first 10 months of life. These patients have tachycardia and tachypnea. No heart murmur is audible in the majority of patients, although gallop rhythm and hepatomegaly are usually present. ECG results showing LVH with “strain” are typical for this condition. Occasionally, myocardial infarction patterns, arrhythmias, and varying degrees of AV block may be seen. Marked generalised cardiomegaly, with normal or congested pulmonary vascularity, is usually present on chest X-rays.

Treatment: digoxin, diuretics, ACE inhibitors.

When proper treatment is given, about one third of patients deteriorate, and die of CHF. Another third survive, but exhibit persistent symptoms, while the remaining third make a complete recovery. Operative procedures are not available.

Kawasaki Disease (mucocutaneous lymph node syndrome)

This is an acute, febrile disease, with skin manifestation in infants and children of preschool age. It comprises vasculitis of the coronary vessels with aneurismatic formation, leading to cicatrization and calcification of affected arteries. Cause of death is heart infarction and high platelet levels, increasing the risk of coronary thrombosis. Kawasaki disease is a multisystemic disease, most likely driven by abnormalities of the immune system, and initiated by an infectious assault.

Clinical manifestation: The onset of illness is abrupt, with a high fever, usually above 39°C. Without treatment, fever persists for an average of 8 days, and is accompanied by: bilateral conjunctivitis; erythema; oedema; desquamation of hands and feet; and a rash. Changes in the lips and oral cavity include: erythema; dryness; fissuring,

peeling, cracking, and bleeding of the lips; “strawberry tongue” (indistinguishable from that of scarlet fever); and diffuse erythema of the oropharyngeal mucosa (Fig. 7). Oral ulceration and pharyngeal exudates are not evident. Cervical lymph node enlargement is the least common of the principal clinical features, occurring in approximately 50% of patients. The firm swelling is usually unilateral, involves more than one node measuring more than 1.5 cm in diameter, and is confined to the anterior cervical triangle.



Figure 7. Typical “strawberry tongue” in patient with Kawasaki disease

In 10-40% of cases, a coronary artery aneurysm developed, with pancarditis, heart infarction, arrhythmia, and heart decompensation.

Laboratory: positive inflammatory parameters; protein and white blood cells in urine; increased activity of factor VIII; increased fibrinogen and beta thromboglobulin.

Present in CBC tests: anaemia, thrombocytosis, and leucocytosis.

In the presence of four or more principal criteria plus fever, diagnosis of Kawasaki disease can be made on day 4 of the illness.

Multiple echo views should be obtained to visualise all major coronary artery segments: left main coronary artery (LMCA), left anterior descending (LAD), left circumflex coronary artery (LCXA), and right coronary artery (RCA). (Fig. 8) According to the new guidelines, aneurysms are classified as secular (almost equal axial and lateral diameters), fusiform (symmetric dilatation with gradual proximal and distal tapering), and ectatic (dilated without segmental aneurysm). A “giant” aneurysm is present when the diameter of the aneurysm is 8 mm or more.

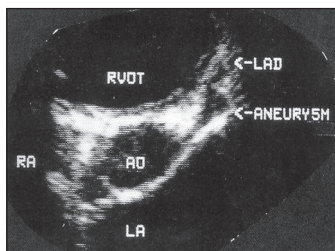


Figure 8. Two echocardiography short axis views: left coronary artery arises from aorta, saccular aneurysms of proximal part of left anterior descedens artery (LAD)

Differential diagnosis

Diseases with similar manifestations must be ruled out through identification of appropriate cultures and the use of laboratory tests:

- Viral infections (e.g., measles, adenovirus, enterovirus, Epstein-Barr virus)
- Scarlet fever
- Staphylococcal scalded skin syndrome
- Toxic shock syndrome
- Bacterial cervical lymphadenopathy
- Drug hypersensitivity reaction
- Stevens-Johnson syndrome
- Juvenile rheumatoid arthritis
- Rocky Mountain spotted fever
- Leptospirosis
- Mercury hypersensitivity reaction (acrodynia)

Treatment

The two main goals of treatment are the reduction of inflammation within the coronary artery and myocardium, and the prevention of thrombosis by inhibiting platelet aggregation.

Immunoglobulin is given in a dose of 2 g/kg IV, with Aspirin 60-100 mg/kg. Aspirin has an anti-inflammatory effect at high doses (80-100 mg/kg/day), and an antiplatelet action at low doses (3-5 mg/kg/day). It should be administered for 6-8 weeks, with repeated ECHO examinations. Infliximab and steroids should be also considered as treatment options for these patients.

Coronarography – classical or MR/CT based – is indicated in infants with: giant aneurysms, signs of ischaemia, positive exercise tests or thallium studies, or heart infarctions.

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