Myocarditis in Children

Hassan Farra, MD

American Board Certified
Pediatrics, Pediatric Cardiology
5/2010
The patient

💔 5 months old previously healthy child comes to the ER with respiratory distress

💔 History of respiratory illness 2 weeks ago
The patient

- RR 60/min, HR 170, BP 80/40
- Pale and cold
- Severe respiratory distress
- 1/6 systolic murmur
- No organomegaly
- Pulses palpable
The patient

♥ Chest X ray cardiomegaly

♥ Echocardiogram: Mildly dilated LV and severe dysfunction. Mitral regurgitation

♥ ECG: Sinus tachycardia. Inverted T waves in the lateral leads
Diagnosis

Myocarditis

Dilated cardiomyopathy
Clues to myocarditis

♥ Acute disease, normal growth, history of viral illness

Clues to DCM

♥ Chronic symptoms, fatigue and SOB, FTT, family hx, other organs involvement
Etiology

♥ Infectious

♥ Immune-mediated

♥ Toxic
Etiology

Infectious

♥ Enteroviruses, especially coxsackie virus B
♥ Adenovirus
♥ Cytomegalovirus
♥ Influenza, parainfluenza
♥ Parvovirus
♥ Measles, rubella, Mumps, arboviruses, Epstein-Barr virus, HIV and hepatitis C virus
Etiology

INFECTIOUS

- **Bacterial**: brucella, Corynebacterium diphtheriae, gonococcus, Haemophilus influenzae, meningococcus, mycobacterium, Mycoplasma pneumoniae, pneumococcus, salmonella, Serratia marcescens, staphylococcus, Streptococcus pneumoniae, Strep. pyogenes, Treponema pallidum, Tropheryma whippelii, and Vibrio cholerae
- **Spirochetal**: borrelia and leptospira
- **Fungal**: actinomyces, aspergillus, blastomyces, candida, coccidioides, cryptococcus, histoplasma, mucormycoses, nocardia, and sporothrix
- **Protozoal**: Toxoplasma gondii and Trypanosoma cruzi
- **Parasitic**: ascaris, Echinococcus granulosus, Paragonimus westermani, schistosoma, Taenia solium, Trichinella spiralis, visceral larva migrans, and Wuchereria bancrofti
- **Rickettsial**: Coxiella burnetii, Rickettsia rickettsii, and Rick. tsutsugamushi
- **Viral**: coxsackievirus, cytomegalovirus, dengue virus, echovirus, encephalomyocarditis, Epstein–Barr virus, hepatitis A virus, hepatitis C virus, herpes simplex virus, herpes zoster, human immunodeficiency virus, influenza A virus, influenza B virus, Junin virus, lymphocytic choriomeningitis, measles virus, mumps virus, parvovirus, poliovirus, rabies virus, respiratory syncytial virus, rubella virus, rubeola, vaccinia virus, varicella–zoster virus, variola virus, and yellow fever virus

Myocarditis. Arthur M. Feldman and Dennis McNamara. NEJM. 19.1388-1398
Etiology

**IMMUNE-MEDIATED**

- **Allergens:** acetazolamide, amitriptyline, cefaclor, colchicine, furosemide, isoniazid, lidocaine, methyldopa, penicillin, phenylbutazone, phenytoin, reserpine, streptomycin, tetanus toxoid, tetracycline, and thiazides
- **Alloantigens:** heart-transplant rejection
- **Autoantigens:** Chagas’ disease, Chlamydia pneumoniae, Churg–Strauss syndrome, inflammatory bowel disease, giant-cell myocarditis, insulin dependent diabetes mellitus, Kawasaki’s disease, myasthenia gravis, polymyositis, sarcoidosis, scleroderma, systemic lupus erythematosus, thyrotoxicosis, and Wegener’s granulomatosis

Myocarditis. Arthur M. Feldman and Dennis McNamara. NEJM. 19.1388-1398
Etiology

TOXIC MYOCARDITIS

♥ **Drugs:** amphetamines, anthracyclines, catecholamines, cocaine, cyclophosphamide, ethanol, fluorouracil, hemetine, interleukin-2, lithium, and trastuzumab

♥ **Heavy metals:** copper, iron, and lead

♥ **Physical agents:** electric shock, hyperpyrexia, and radiation

♥ **Miscellaneous:** arsenic, azides, bee and wasp stings, carbon monoxide, inhalants, phosphorus, scorpion bites, snake bites, and spider bites

Myocarditis. Arthur M. Feldman and Dennis McNamara. NEJM. 19.1388-1398
Pathophysiology

- The virus spreads via the blood stream to the myocardium
- Lymphocytic infiltration and myocyte necrosis ensue
- The myocardium is infiltrated with T lymphocytes and macrophages while the B lymphocytes and natural killer cells are absent.
- Viral damage is minimized both by a direct cardioprotective effect of these substances and by enhanced recruitment/activation of mononuclear cells.
- Viral invasion of the myocardium is associated with direct destruction of myocytes, but it is the release of cytokines into the circulation which results in decreased myocardial performance. Cytokines such as tumor necrosis factor-α (TNFα), interleukin-1α and interleukin-1β are produced in large quantities by immune cells and the myocardium.

Kawai C. From myocarditis to cardiomyopathy: mechanisms of inflammation and cell death: learning from the past for the future. Circulation 1999;99:1091-100.
Signs & Symptoms

♥ Flu-like illness (fever, rhinorrhea, or GI disturbance)

♥ After the subsidence of symptoms of a systemic illness, patients frequently present with symptoms of acute heart failure, arrhythmias, syncope and sudden death

♥ Respiratory distress or GI symptoms may be the most prominent signs
Signs & Symptoms

♥ Resting tachycardia

♥ Third heart sound

♥ Murmur of mitral regurgitation

♥ CXR shows cardiomegaly and edema but in acute fulminant myocarditis the heart size can be normal

♥ ECG changes are ST segment flattening and T wave inversion, with low QRS
Echocardiogram

❤ Depressed ejection fraction
❤ Increased left ventricular end-diastolic dimension
❤ Increased wall thickness
❤ Mitral regurgitation

Labs

♥ ABG: Metabolic acidosis and compensatory respiratory alkalosis
♥ Elevated liver enzymes
♥ Borderline urea and creatinin
♥ Elevated CPK and Troponin
Labs

 ♥ Viral serologies and cultures

 ♥ Recovery of virus from myocyte culture, in situ hybridization or by PCR
DCM labs

 ♥ CBC, lytes, urea, creatinin, glucose, LFTs, cholesterol, BNP
 ♥ Alk Phos, Calcium, phosphorus, Mg
 ♥ Thyroid, Uric acid, ABG, gap, troponin, CPK
 ♥ UA, ketones in the urine
 ♥ Metabolic:
   – Lactate, Pyruvate, Ammonia, Total free carnitine and acylcarnitine. Urine organic acid screen
Diagnosis

♥ Endomyocardial biopsy

♥ MRI with contrast
Pathology

♥ Gold standard

♥ Dallas criteria

♥ Definitive: lymphocytic infiltration with myocyte necrosis

♥ Borderline: lymphocytic infiltration with interstitial edema

Figure 1. Histopathological Appearance of Normal Myocardium (Panel A, ×100), Borderline Myocarditis (Panel B, ×100; Panel C, ×300), and Active Myocarditis (Panel D, ×100; Panel E, ×300), According to the Dallas Criteria, on Staining with Hematoxylin and Eosin.
Endomyocardial biopsy of the right ventricle showing acute diffuse myocarditis. There is prominent myofiber necrosis and loss in association with a high-grade mononuclear infiltrates.
Pathology

♥ Eosinophilic

♥ Giant cell myocarditis

Pathology

Eosinophilic myocarditis

♥ May be attributed to eosinophilic syndromes or allergic reactions
♥ Responds to treatment of the eosinophilic disorder and/or withdrawal of the offending agent

Giant cell myocarditis

♥ Poor prognosis
♥ May respond to aggressive immunosuppressive therapy

Biopsy

Arguments in Favor of Biopsy

♥ Diagnosis and treatment:
  – To differentiate between viral myocarditis and cardiomyopathy.

♥ Prognosis:
  – The outcome with viral myocarditis is better than that with dilated cardiomyopathy, especially in children.

♥ Decision algorithm for Transplant and/or Mechanical Circulatory Support:

Biopsy

Arguments Against Biopsy

♥ High Incidence of False-Negative Results:
- The disease may be focal.
- variability (disagreement of 40%) amongst expert pathologists evaluating the same biopsy specimens.

♥ Potential Risk:
- myocardial perforation and arrhythmias

♥ Lack of Evidence for Immunosuppressive Therapy Efficacy:
- Immunosuppressive therapy is not a proven therapy

Desmond Bohn and Lee Benson.
Diagnosis and Management of Pediatric Myocarditis.
The patient

♥ Intubated and ventilated
♥ Sedated and muscle relaxed
♥ Central venous line, arterial line and Foley catheter inserted
♥ Milrinone and Furosemide started
Treatment

♥ Mechanical Ventilation
♥ Sedation/Muscle relaxation
♥ Inotropes
♥ Reduce preload and after load
Ventilation

♥ Raised intrathoracic pressure reduces transmural myocardial wall tension and left ventricular afterload
Hemodynamics

- Low cardiac index
- Elevated pulmonary wedge pressure
- High systemic vascular resistance
Phosphodiesterase inhibitors

♥ Amrinone, milrinone, and enoximone
♥ Decrease the rate of cAMP degradation
♥ Enhanced calcium influx into the cell
♥ Increased contractility
♥ Systemic arterial and venous dilation
♥ Improves relaxation
♥ Less arrhythmias
♥ Can be given peripherally
♥ Safer on the floor
The patient

♥ Started to develop renal failure
♥ Elevated urea and creatinin and decreased UOP
♥ Electrolytes normal
♥ Nephrology consultation
♥ ATN: Increase diuretics, fluid restriction, electrolytes monitoring
Diuretics

Furosemide, Bumetanide
Chlorothiazide, Hydrochlorothiazide
Metolazone
Spironolactone
Mannitol
Neseritide

- Recombinant human BNP Natriuretic peptide
- Diuresis and natriuresis
- Vasodilator
- Suppress the neurohormonal activation
- Indirect increase in cardiac output
- Potential adverse impact on mortality rate and a potential risk of worsening renal function
The patient

♥ Had an episode of ventricular fibrillation

♥ Shocked once successfully and started on Amiodarone
The patient

♥ Renal failure peaked and then started to improve

♥ The patient was extubated after 1 week

♥ IV meds were changed to oral
The patient

♥ Discharged home on Digoxin, Enalapril, Lasix and Amiodarone after 2 weeks
Treatment

♥ Carnitine
♥ Anticoagulation
♥ Immunomodulators
♥ Antivirals
♥ Interferons
♥ Mechanical Support
Immunosuppression

_randomized 111 patients to receive either conventional medical therapy alone or combined with prednisone and either azathioprine or cyclosporin.

No difference in the left ventricular ejection fraction.

No difference in survival.

**Figure 1.** Mean (±SE) Left Ventricular Ejection Fraction (LVEF) in the Immunosuppression and Control Groups at Base Line, Week 28, and Week 52.

Panel A shows the mean values for all available studies at each time, with the numbers of patients indicated at the bottom of the panel. There was no difference between the two groups in the mean LVEF at base line, week 28, or week 52 (P = 0.97, P = 0.95, and P = 0.45, respectively). Panel B shows the mean values for the 78 patients in whom data were available at all three times. Again, there was no significant difference between the groups (P = 0.51, P = 0.60, and P = 0.50, respectively).

**Figure 2.** Actuarial Mortality (Defined as Deaths and Cardiac Transplantations) in the Immunosuppression and Control Groups.

The numbers of patients at risk are shown at the bottom. There was no significant difference in mortality between the two groups.
IVIG

♥ Enhancement of viral clearance or down-regulation of inflammation

♥ Only one trial randomized 62 patients to a therapy with gammaglobulin or control

♥ No change in EF was seen after 12 months

IVIG

◆ One case-control trial

◆ Improved recovery of LV function with IVIG and a trend to a better survival at 1 year


♥ Probably beneficial in neonatal and pediatric myocarditis
Antivirals

♥ Pleconaril for enteroviruses
♥ Cidofovir for adenoviruses
♥ Neuraminidase inhibitors for influenza viruses
♥ Gancyclovir for cytomegalovirus
ECMO

♥ Pump and oxygenator
♥ Most common device in children
♥ Cannulation from the neck or the groin
♥ Risk of bleeding, thrombosis and infection
♥ Not a long term therapy
♥ Needs a highly trained team
ECMO
VAD

♡ Only pump
♡ Most common device in adults
♡ Cannulation from the chest
♡ Same risks as in ECMO
♡ Long term therapy in adults
♡ Limited to older children
♡ Smaller devices are available in Europe
Figure 2. The HeartMate left ventricular assist device.
VAD

(Circulation. 2006;113:147-155.)
Heart Transplant

1-year survival after heart transplantation in children is 85%

Survival 20 years after transplantation is 40%

Circ Heart Fail. 2009;2:490-498
The patient

♥ Cardiac function improved gradually over the next few months

♥ By 6 months the cardiac evaluation was normal and the patient off meds
Prognosis

♥ The natural history is better in children

♥ Most of the patients who survive the acute phase seem to have restoration of normal cardiac function

Prognosis

♥ The overall survival in children with acute myocarditis who reach hospital alive can be as high as 80%

THANK YOU