Myocarditis in infants and children: A review for the paediatrician

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Clinical myocarditis is uncommon in infants and children. The most common pathogen is Coxsackievirus B. The offending agent triggers an immune response, which results in myocardial edema with subsequent impairment of systolic and diastolic function. Newborns and infants are more severely affected because the immature myocardium has limited ways of adapting to an acute insult. Children typically present with sinus tachycardia and gallop on auscultation, cardiomegaly on chest x-ray and small voltages on electrocardiogram. The echocardiogram shows reduced ventricular function. Viral studies can isolate the pathogen. Myocardial biopsy is useful diagnostically, but carries a significant risk for the sick infant. The first line of treatment includes measures such as rest, oxygen and diuretics. Inotropic agents are useful in moderate to severe heart failure. The role of immunosuppressive therapy is not yet clearly established in the paediatric age group. Prognosis is guarded in newborns but more favourable in older children.

Key Words: *Children; Infants; Myocarditis*

La myocardite chez les nourrissons et les enfants : Une révision pour le pédiatre

RÉSUMÉ : La myocardite clinique est rare chez les nourrissons et les enfants. Le pathogène le plus courant est le virus Coxsackie B. L'agent déclenchant provoque une réaction immunitaire qui entraîne un œdème du myocarde suivi d'une défaillance de la fonction systolique et diastolique. Les nouveau-nés et les nourrissons sont plus touchés parce que le myocarde immature possède peu de moyens de s'adapter à une insulte aiguë. D'ordinaire, les enfants présentent une tachycardie sinusale et un bruit de galop à l'auscultation, une cardiomégalie à la radiographie pulmonaire et une faible tension à l'électrocardiogramme. L'échocardiogramme révèle une réduction de la fonction ventriculaire. Les études virales peuvent isoler le pathogène. La biopsie du myocarde est utile d'un point de vue diagnostique, mais comporte un risque important pour l'enfant malade. Le traitement de première ligne inclut des mesures comme le repos, l'oxygène et les diurétiques. Des agents inotropes sont utiles en cas de défaillance cardiaque modérée à grave. Le rôle d'un traitement aux immunosuppresseurs n'est pas encore clairement établi dans la population pédiatrique. Le pronostic est réservé chez les nouveau-nés, mais plus favorable chez les enfants plus âgés.

Myocarditis is defined as inflammation of the myocardium. Clinically, the manifestation of myocarditis is relatively uncommon in infants and children. It represented only 0.3% of 14,322 patients seen over a 23-year period at Texas Children's Hospital, Houston, Texas (1). Subclinical myocarditis is much more prevalent. On the other hand, classic histological features of myocarditis have been documented in infants and children who were victims of sudden unexpected death (2).

EPIDEMIOLOGY AND ETIOLOGY

The majority of cases of myocarditis are secondary to a viral infection. The most common agent in children is Coxsackievirus B, in particular serotypes 1 to 6 (3,4). Coxsackievirus B is usually responsible for sporadic cases, although outbreaks have been reported (5). Other enteroviruses (6), influenza (7), rubella (8) and adenoviruses (9), and a host of other agents, have also been implicated in cases of myocarditis (Table 1).

PATHOLOGY

At gross examination, the myocardium appears pale and flabby. The ventricular cavities are dilated, with wall thinning and an increase in myocardial mass. A mural thrombus is occasionally present.

Microscopic inspection demonstrates a predominantly mononuclear inflammatory cell infiltrate. Interstitial edema and, in more severe cases, myocyte necrosis are present.

Experiments in murine models have shown that myocarditis is an immune process that is triggered by a locally produced neoantigen (10,11). Cell-mediated cytotoxicity carried out by cytotoxic T cells and natural killer cells is the primary pathological process, with humoral defences contributing to the insult (12,13). The immune response is modulated by locally produced cytokines that play an important role in the development of chronic myocarditis (14).

PATHOPHYSIOLOGY

The primary pathophysiological processes are the development of myocardial necrosis and interstitial edema,

TABLE 1: Some causes of myocarditis	
Viral	**Parasitic**
Coxsackievirus B	*Toxocara canis*
Coxsackievirus A	Schistosomiasis
Adenoviruses	Cystercosis
Echoviruses	Visceral larva migrans
Hepatitis viruses	**Fungal**
Herpes simplex virus	Histoplasmosis
Epstein-Barr virus	Candida
Cytomegalovirus	**Drugs**
Polio viruses	Amphotericin B
Varicella virus	Tetracycline
Influenza viruses	Sulfonamides
Bacterial	Phenylbutazone
Diphtheria	Cyclophosphamide
Salmonella	**Autoimmune**
Leptospira	Systemic lupus erythematosus
Streptococcus	Rheumatic fever
Mycoplasma bacteria	Ulcerative colitis
Legionella	Rheumatoid arthritis
Rickettsial	**Other**
Rickettsia ricketsii	Sarcoidosis
Protozoal	Idiopathic
Trypanosoma cruzi	

with consequent impairment in the contractile performance of the heart muscle. Chamber dilation and thinning of the ventricular wall increases wall tension, augments myocardial oxygen demand and stimulates hypertrophy. Preload reserve is minimal in the immature myocardium, and the maintenance of an adequate cardiac output in the face of failing contractility is dependent on chronotropic upregulation. Comorbid fever and anemia can place further stress on the heart. When compensatory mechanisms are depleted, the heart fails, resulting in a low output state. A decrease in cardiac compliance, along with incomplete emptying of the left ventricle, raises left ventricular diastolic and pulmonary venous pressures, and predisposes patients to pulmonary edema.

In the majority of cases, the myocardial insult is limited, and the heart recovers normal function within months. When myocardial damage is more extensive, scar tissue replaces necrotic myocardium during healing, and the recovery of function is incomplete.

CLINICAL PRESENTATION

Dyspnea with feeding, vomiting and pallor are common presenting complaints in infants. Older children present with a marked decrease in stamina and shortness of breath in the context of a viral infection. Com-plaints of palpitation suggest coexistent arrhythmia. Chest pain is nonspecific and indicates a possible associated pleural or pericardial inflammation.

On physical examination, the child is tachypneic, tachycardic and febrile. Hypotension suggests severely depressed cardiac function. Pallor and peripheral vasoconstriction due to sympathetic activation are usually noted. Peripheral capillary refill is delayed. In children, the earliest sign of fluid retention secondary to congestive heart failure is eyelid puffiness. More severe failure presents with hepatomegaly and generalized edema. A pericardial rub and distant heart sounds suggest the presence of an associated pericardial effusion. A soft first heart sound is common but nonspecific and often difficult to appreciate in the tachycardic infant. A gallop rhythm produced by a third heart sound is frequent and best heard at the apex. A high pitch regurgitant murmur detected at the apex indicates coexistent mitral insufficiency.

DIFFERENTIAL DIAGNOSIS

Sepsis, severe dehydration or anemia should be considered as diagnostic possibilities in the ill neonate or infant. Primary endocardial fibroelastosis and metabolic dilated cardiomyopathy are myocardial disorders that can present in a similar fashion. Congenital structural lesions, such as critical coarctation of the aorta or anomalous origin of the left coronary artery from the pulmonary artery, must be ruled out.

DIAGNOSIS

The chest x-ray classically displays cardiomegaly and pulmonary venous congestion. An associated pericardial effusion can accentuate the degree of cardiomegaly.

The 12-lead electrocardiogram typically shows sinus tachycardia and low voltage QRS complexes (less than 5 mm total amplitude in all limb leads), with low-amplitude or slightly inverted T waves, and a small or absent Q wave in leads V5 and V6. PR and QT interval prolongation are common but nonspecific.

The presence of arrhythmia in the context of a febrile illness should point the clinician to the possibility of myocarditis. Paroxysmal atrial tachycardia (15), ventricular ectopy (16-18) and various degrees of heart block (19) have all been described in association with myocarditis.

The echocardiogram is essential in the diagnosis and follow-up of myocarditis. Structural heart disease and pericarditis can be readily ruled out. Myocardial function is assessed at the time of diagnosis, and serves as a baseline for future monitoring of disease progression and response to therapeutic interventions.

Isolation of the offending virus from stool, throat washings or blood is possible early in the disease (20). Otherwise, serological diagnosis relies on a fourfold increase in virus-specific antibody titres between acute and convalescent blood samples.

The role of myocardial biopsy in establishing the diagnosis of myocarditis is controversial. Endomyocardial biopsy can establish the diagnosis and degree of involvement (21). Polymerase chain reaction performed on myocardial tissue has been recently shown to be both sensitive and specific to the diagnosis of enteroviral and adenoviral myocarditis (9). The utility of biopsy must be weighed against the risk of perforation and death, particularly in the ill infant (22). In addition, patchy right ventricular disease or isolated left ventricular involvement can escape detection when random biopsy samples are limited to the right ventricular septum.

TREATMENT

Treatment of the infant and child affected by myocarditis is tailored to the severity of disease. The child is hospitalized, and telemetry is implemented when coexistent arrhythmia is present. Ancillary therapeutic measures include supplemental oxygen, diuretics and bed rest. Anemia is corrected whenever present. Fluid and salt intake are controlled. For more severe disease, an inotropic agent, such as dopamine or dobutamine, is added, especially if cardiac function is depressed on echocardiogram. Administration of these drugs requires admission to the intensive care unit and intravascular blood pressure monitoring. Nitroprusside, an intravenous afterload-reducing agent, can be considered in the absence of hypotension. Digitalis should be used with extreme care during the acute phase of the disease because its enhanced activity on the inflamed myocardium can precipitate serious dysrhythmia (23). If myocarditis results in dilated cardiomyopathy and chronic heart failure, digoxin and an angiotensin-converting enzyme inhibitor are therapeutically useful (24).

The administration of immunosuppressive agents in the acute treatment of myocarditis in children is controversial. The small cohort sizes in most paediatric studies, and the lack of large double-blind controlled trials prohibit any clear-cut recommendations. Steroids, azathioprine and gamma globulins have been used with variable success reported. In the Myocarditis Treatment Trial, mostly adult patients treated with azathioprine and prednisone or with cyclosporine and prednisone did not fare any better than patients treated with conventional treatment alone (25). In a smaller paediatric study, patients treated with immunosuppressive agents did better than patients treated with conservative measures alone (26). There have been some recent encouraging results with the use of gamma globulin (27,28).

PROGNOSIS

Myocarditis has an ominous prognosis in newborns, with 75% mortality when Coxsackievirus B is the suspected pathogen (29). Older children fare better; mortality is less than 25%, while another 25% of children will suffer from chronic symptoms of heart failure. Recovery is complete in about one-half of diagnosed cases (30).

REFERENCES

1. Friedman RA, Schowengerdt KO Jr, Towbin JA. Myocarditis. In: Garson A Jr, Bricker JT, Fisher DJ, Neish SR, eds. The Science and Practice of Pediatric Cardiology, 2nd edn. Baltimore: Williams & Wilkins, 1998:1777-94.
2. Burch GE, Sun SC, Chu KC, Sohal RS, Colcolough HL. Interstitial and Coxsackie virus B myocarditis in infants and children: A comparative histologic and immunofluorescent study of 50 autopsied hearts. JAMA 1968;203:1-8.
3. Dery P, Marks MI, Shapera R. Clinical manifestations of coxsackie virus infections in children. Am J Dis Child 1974;128:464-8.
4. Hosier DM, Newton WA Jr. Serious Coxsackie infection in infants and children. Am J Dis Child 1958;96:251-67.
5. Helin M, Savola J, Lapinleimu K. Cardiac manifestations during a coxsackie B5 epidemic. BMJ 1968;2:97-9.
6. Lerner AM, Wilson FM, Reyms MP. Enterovirus and the heart (with special emphasis on the probable role of coxsackieviruses, group B, types 1-5). Mod Concepts Cardiovasc Dis 1975;64:7-10.
7. Karjalainen J, Nieminen MS, Heikkila J. Influenza A1 myocarditis in conscripts. Acta Med Scand 1980;20:27-30.
8. Ainger LE, Lawyer NG, Fitch CW. Neonatal rubella myocarditis. Br Heart J 1966;28:691-7.
9. Martin AB, Webber S, Fricker FJ, et al. Acute myocarditis. Rapid diagnosis by PCR in children. Circulation 1994;90:330-9.
10. Woodruff JF. Viral myocarditis: A review. Am J Pathol 1980;101:425-84.
11. Godeny EK, Gauntt CJ. Murine natural killer cells limit Coxsackievirus B3 replication. J Immunol 1987;139:913-8.
12. Wong CY, Woodruff JJ, Woodruff JF. Generation of cytotoxic T lymphocytes during coxsackie B-3 infection. II. Characterization of effector cells and demonstration of cytotoxicity against viral-infected myofibers1. J Immunol 1977;118:1165-9.
13. Maisch B, Trostel-Soeder R, Stechemesser E, Berg PA, Kochsiek K. Diagnostic relevance of humoral and cell-mediated immune reactions in patients with acute viral myocarditis. Clin Exp Immunol 1982;48:533-45.
14. Kroemer G, Martinez AC. Cytokines and autoimmune disease. Clin Immunol Immunopathol 1991;61:275-95.
15. Cherry JD, Jahn Cl, Meyer TC. Paroxysmal atrial tachycardia associated with echo 9 virus infection. Am Heart J 1967;73:681-6.
16. Huang M, Bigos D, Levine M. Ventricular arrhythmia associated with respiratory syncytial viral infection. Pediatr Cardiol 1998;19:498-500.
17. Balaji S, Wiles HB, Sens MA, Gillette PC. Immunosuppressive treatment for myocarditis and borderline myocarditis in chldren with ventricular ectopic rhythm. Br Heart J 1994;72:354-9.
18. Friedman RA, Kearney DL, Moak JP, Fenrich AL, Perry JC. Persistence of ventricular arrhythmia after resolution of occult myocarditis in children and young adults. J Am Coll Cardiol 1994;24:780-3.
19. Schieken RM, Myers MG. Complete heart block in viral myocarditis. J Pediatr 1975;87:831-2.
20. Berkovich S, Rodriquez-Torres R, Lin JS. Virologic studies in children with acute myocarditis. Am J Dis Child 1968;115:207-12.
21. Fenoglio JJ Jr, Ursell PC, Kellogg CF, Drusin RE, Weiss MB. Diagnosis and classification of myocarditis by endomyocardial biopsy. N Engl J Med 1983;308:12-8.
22. Pophal SG, Sigfusson G, Booth KL, et al. Complications of endomyocardial biopsy in children. J Am Coll Cardiol 1999;34:2105-10.
23. Matsumori A, Igata H, Ono K, et al. High doses of digitalis increase the myocardial production of proinflammatory cytokines and worsen myocardial injury in viral myocarditis: A possible mechanism of digitalis toxicity. Jpn Circ J 1999;63:934-40.
24. Lewis AB, Chabot M. The effect of treatment with angiotensin-converting enzyme inhibitors on survival of pediatric patients with dilated cardiomyopathy. Pediatr Cardiol 1993;14:9-12.
25. Mason JW, O'Connell JB, Herkowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. N Engl J Med 1995;333:270-5.
26. Camargo PR, Snitcowsky R, da Luz PL, et al. Favorable effects of immunosuppressive therapy in children with dilated cardiomyopathy and active myocarditis. Pediatr Cardiol 1995;16:61-8.
27. Drucker NA, Colan SD, Lewis AB, et al. Gamma-globulin treatment of acute myocarditis in the pediatric population. Circulation 1994;89:252-7.
28. Lee KJ, McCrindle BW, Bohn DJ, et al. Clinical outcomes of acute myocarditis in childhood. Heart 1999;82:226-33.
29. Kibrick S, Benirschke K. Severe generalized disease (encephalohepatomyocarditis) occuring in the newborn period and due to infection with coxsackievirus group B. Evidence of intrauterine infection with this agent. Pediatrics 1958;22:857-74.
30. Hastreiter AR, Miller RA. Management of primary endomyocardial disease: The myocarditis-endocarditial fibroelastosis syndrome. Pediatr Clin North Am 1964;11:401-30.