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G. R. Noren,[1] *M.D.; N. A. Staley,*[2] *M.D.; C. M. Bandt,*[3] *M.D.; and E. L. Kaplan,*[1] *M.D.*

Occurrence of Myocarditis in Sudden Death in Children

In recent years, there has been increasing interest in the natural history and pathophysiology of nonrheumatic inflammatory disease of the heart in children. However, because of the wide spectrum of clinical presentations and the difficulty in establishing a rapid, definitive diagnosis, the prevalence of myocarditis in any given population remains speculative. Therefore, by necessity, most studies expressing the incidence of myocarditis are derived from retrospective reviews of necropsy material. In one such review, Gore and Saphir [*1*] identified 1402 cases of myocarditis in 40 000 hospital necropsies for an overall prevalence of 3.5%. Seventy of these cases were associated with viral illness, and an additional 80 cases of isolated myocarditis were presumed to have been of viral etiology, therefore giving a maximal autopsy diagnosis of viral myocarditis in this group of 0.38%. In another study, Gormsen [*2*] identified only 17 cases of myocarditis in 1378 cases of sudden unexpected death (1.2%), but histologic examination had been carried out in only 117 of these cases. In studies of aircraft-related accidents, Stevens et al and Sopher [*3,4*] have postulated that the incidence of focal myocarditis in the adult population may be as high as 5%.

We were unaware of any comparable data in children; therefore, we undertook a three-year retrospective study of children who died suddenly and whose deaths were reviewed at a medical examiner's office.

The presence of myocarditis in children dying a violent death (accidents, homicide, or suicide) was compared to the occurrence of myocarditis in children whose death was sudden and unexpected. Children dying a violent death were selected for review as being representative of the general population. The comparison group of sudden, unexpected deaths was used to examine the extent of myocarditis in this population of children and its possible role as an etiologic factor in some of these deaths.

Materials and Methods

A total of 6082 deaths were investigated by the Hennepin County Medical Examiner's Office during the years 1972 through 1974. Of these, 353 deaths or 5.2% occurred in

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[1] Department of Pediatrics, Hennepin County Medical Center and University of Minnesota, Minneapolis, Minn. 55415.

[2] Department of Pathology, Minneapolis Veterans Administration Hospital and University of Minnesota, Minneapolis, Minn. 55415.

[3] Department of Pathology and Medical Examiners Office, Hennepin County Medical Center, 5th St. and Portland Ave., South, Minneapolis, Minn. 55415.

children through the age of 16 years. Accidents were responsible for the greatest number of the childhood deaths (174 or 49.3%). Homicides accounted for 24 deaths (6.8%) and suicides for 16 deaths (4.5%); there were 115 sudden deaths that were classified as unexpected by historical data (32.6%). The remaining deaths were secondary to causes that were easily explained by usual autopsy procedures. Therefore, 329 (93%) cases were initially accepted for this review.

Histologic sections of the myocardium were available from 90 of the 115 sudden and unexpected deaths. In the violent death group, only 48 of 214 cases were accepted or available for histologic review. If intensive medical or surgical care occurred prior to death, the case was not accepted for review. Also, in many instances, because of the nature of the violent death, full necropsy examination was not deemed necessary by the medical examiner and no myocardial tissue was available.

When myocardial tissue was available, sections from the free wall of both the left and right ventricles were stained with hematoxylin and eosin, elastic van Gieson solution, and Masson's trichrome for the evaluation of necrosis, inflammatory infiltrate, and fibrosis. Viral cultures or viral antibody titers were not routinely performed by the medical examiner's office on the patients included in this series. Where indicated, toxicology studies were done on the children dying suddenly and unexpectedly. Criterion for the diagnosis of myocarditis by histologic examination was defined as one or more areas of inflammation characterized by infiltrates of at least 20 inflammatory cells with or without associated necrosis or fibrosis.

Results

Of the total number of cases reviewed by histologic examination, 17 of the 138 or 12.3% revealed evidence of active or healing myocarditis (Table 1). Fifteen of the 17 cases with histologic evidence of myocarditis occurred in the 90 children who died suddenly

TABLE 1—*Medical examiner's cases, ages 0 to 16 years.*

Type of Death, no.	Reviewed by Histology, no.	Histologic Myocarditis, no.	Histologic Myocarditis, %
Violent (accident, homicide, suicide), 214	48	2	4.2
Sudden and unexpected, 115	90	15	16.7
Total, 329	138	17	12.3

and unexpectedly (16.7%). Seventy-nine of these children were less than 1 year of age at the time of death and 8 (10%) of the 79 had evidence of myocarditis. In contrast, of the 11 children between the ages of 1 and 16 years, 7 (64%) had histologic evidence of myocarditis. Age of death in the sudden and unexpected death group with myocarditis was 0 to 1 year, 8 children; 1 to 5 years, 3 children; 6 to 10 years, 1 child; and 11 to 16 years, 3 children (Table 2).

Only 2 (4.2%) of the 48 children dying a violent death secondary to accident, homicide, or suicide had histologic evidence of myocarditis. These children were 11 and 15 years of age (Cases 16 and 17).

Eleven of the 17 children with histologic evidence of myocarditis died during the winter months, with one death occurring in December, three in January, three in February, and four in March. There was one death in May, two in July, two in September, and one in October.

The 17 children who had microscopic evidence of myocarditis displayed a wide

TABLE 2—*Details of 17 cases with histologic evidence of myocarditis.*

Patient	Age	Sex	Clinical History	Significant Necropsy Findings
1	19 days	m	well child found dead in crib	intra-alveolar blood of undetermined origin; pulmonary congestion; focal area of 40–60 interstitial lymphocytes in left ventricular myocardium; 2 heart blocks
2	27 days	f	well child found dead in crib	pulmonary edema; focal areas of 20–40 lymphocytes in myocardium and associated with myocardial necrosis; 2 heart blocks
3	30 days	m	mild respiratory infection for 2 days prior to being found dead in crib	petechial hemorrhage in pleura and epicardium with some pulmonary congestion; focal infiltrates of over 60 lymphocytes in pericardium and myocardium; 3 heart blocks
4	1½ months	m	respiratory infection for 2 days prior to being found dead in crib	focal areas of 40–60 interstitial lymphocytes in the left ventricular myocardium; moderate endocardial fibroelastosis of the inflow and outflow tracts of the left ventricle; 3 heart blocks
5	1½ months	f	respiratory infection for 3 days prior to being found dead in crib; chest X-ray negative 2 days prior to death	small bronchi contained mucoid material with variable number of phagocytes; no obstruction or atelectasis noted; pericardial and myocardial infiltrates of 60–100 lymphocytes; 2 heart blocks
6	7 months	m	respiratory infection for 1 week prior to being found dead in bed	lobar pneumonia with myocardial foci of interstitial lymphocytic infiltrates associated with myocardial necrosis; 2 heart blocks
7	8½ months	f	no history of preceding illness; "functional" heart murmur known since age 6 weeks	interstitial pulmonary infiltrates; small patent ductus arteriosus and left ventricular hypertrophy; myocardial foci of 40–60 interstitial lymphocytes; left ventricular endocardial fibroelastosis; 4 heart blocks
8	1 year	f	fever and diarrhea for 3 days prior to being found dead in bed	mild hypotonic dehydration by vitreous humor electrolytes; minimal aspiration pneumonia; focal areas of greater than 100 interstitial lymphocytes in the myocardium; 2 heart blocks
9	1½ years	f	fever and diarrhea for 3 days prior to being found dead in bed	pulmonary edema; focal areas of greater than 100 interstitial lymphocytes in the myocardium; 2 heart blocks
10	2 years	m	no history of preceding illness	pulmonary congestion and edema with minimal amounts of mucous in terminal bronchi; focal myocardial infiltrates of 40–80 lymphocytes with tinctorial changes in the surrounding myocytes; 2 heart blocks

TABLE 2—*Details of 17 cases with histologic evidence of myocarditis.*

Patient	Age	Sex	Clinical History	Significant Necropsy Findings
11	3 years	f	mild respiratory infection for 2 days prior to cardiac arrest in physician's office	pulmonary edema and focal pulmonary hemorrhage; focal myocardial infiltrates of 50–100 interstitial lymphocytes associated with myocardial necrosis, 2 heart blocks
12	7 years		upper respiratory infection for 3 weeks prior to death; dyspnea and and chest pain a few hours prior to death	focal peribronchial infiltrates of eosinophils; few areas of atelectasis; myocardium revealed diffuse intense infiltrates of eosinophils, plasma cells, histiocytes, and lymphocytes; occasional giant cells were seen; 5 heart blocks
13	14 years	f	no history of preceding illness; found dead on commode by mother	pulmonary edema; focal myocardial infiltrates of 40–60 interstitial lymphocytes; 2 heart blocks
14	15 years	m	sore throat 3 weeks prior to death; history of chest pain on day before death; collapsed at desk in school	multiple renal cysts; small quantity of gastric debris within tracheal bronchial tree; myocardium showed extensive irregular areas of fibrosis; this was present within the septum and adjacent to or perhaps within the bundle of His; other areas demonstrated interstitial edema and lymphocytes; 5 heart blocks
15	16 years	m	no history of preceding illness	sections of lung showed extensive areas in which the alveola contained protein-rich edema fluid and erythrocytes; focal myocardial infiltrates of 20–60 interstitial lymphocytes; 4 heart blocks
16	11 years	m	gunshot wound to head; homicide	myocardial foci of 20–60 interstitial lymphocytes; 2 heart blocks
17	15 years	m	mental health patient who jumped from third floor of hospital; suicide	ruptured spleen; multiple skull fractures; epidural-subdural-subarachnoid hemorrhage; early bronchopneumonia; foci of pericardial lymphocytic infiltrates; foci of 20–40 myocardial lymphocytic infiltrates; 2 heart blocks

spectrum of histologic findings (Table 2). At one end of the spectrum was the finding of focal areas of 40 to 100 interstitial cells which were predominantly mononuclear. These focal areas were usually associated with tinctorial changes in the surrounding myofibers. Occasionally there was concomitant necrosis of the myocardial cells (Fig. 1). In others there was the finding of many areas of more than 100 inflammatory cells, again predominantly mononuclear (Fig. 2), while at the other end of the spectrum was the observation of myocardial fibrosis (Fig. 3) or left ventricular endocardial fibroelastosis in association with areas of mononuclear cell infiltrates, or both.

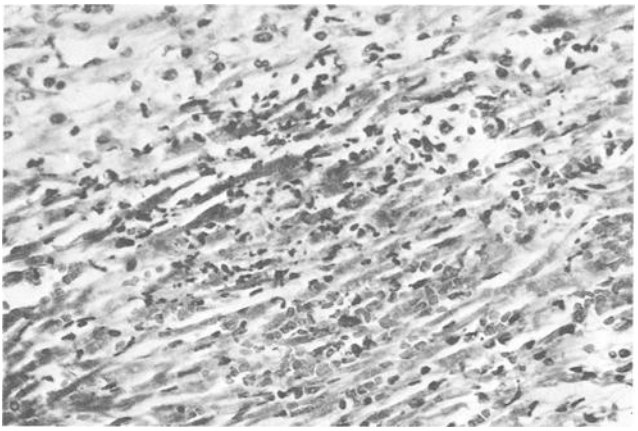

FIG. 1—*Myocardium of a 27-day-old girl (Case 2) who was found dead in her crib without a history of preceding illness. This section demonstrates a focal area of myocytolysis and necrosis with lymphocytic infiltrates (hematoxylin and eosin stain).*

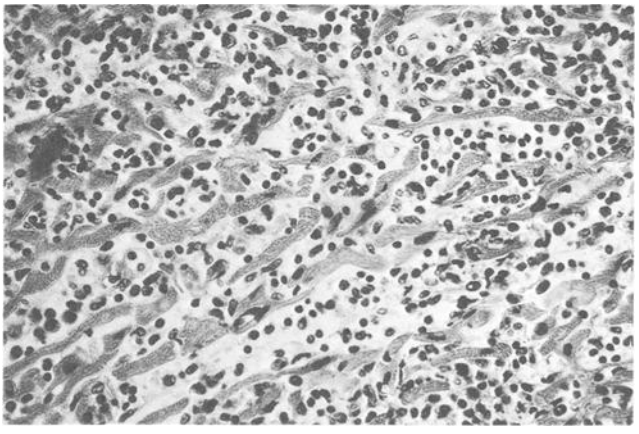

FIG. 2—*Photomicrograph of the myocardium of a 7-year-old girl (Case 12) who had a history of an upper respiratory infection three weeks prior to her sudden and unexpected death. This section shows a dense myocardial infiltrate consisting chiefly of eosinophils with some plasma cells, histiocytes, and lymphocytes being observed (hematoxylin and eosin stain).*

Associated findings at necropsy in the children dying a sudden, unexpected death included pulmonary congestion, probable viral pneumonia (3 cases), left ventricular endocardial fibroelastosis (2 cases), massive myocardial fibrosis (1 case), and a small patent ductus arteriosis (1 case) (Table 2).

Postmortem viral antibody titers were done in two children with myocarditis. Both were over the age of one year. An adenovirus titer of 1:32 was demonstrable in one (Case 12, Fig. 2), while in the other neutralizing antibody to coxsackievirus B4 in the 19 S serum fraction was 1:32 while the total neutralizing antibody titer for coxsackievirus B4 was 1:256 (Case 14, Fig. 3).

When performed, toxicology analysis was negative, and in none of the 17 children with myocarditis was there evidence of bacterial infection by routine culture techniques.

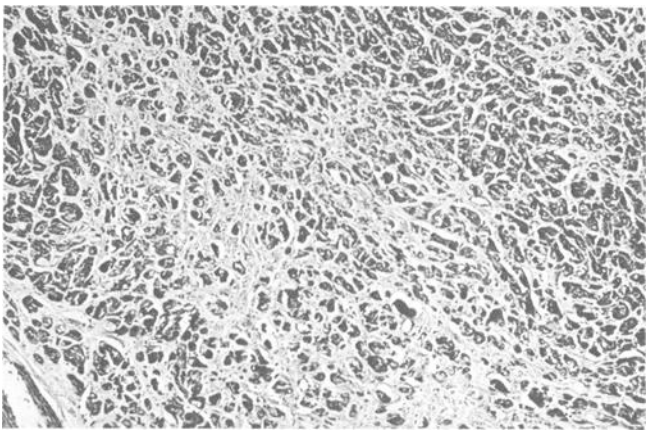

FIG. 3—*Photomicrograph of the myocardium of a 15-year-old boy (Case 14) who was well until 3 weeks prior to his death when he developed a sore throat. This boy suddenly collapsed at his desk in school. This section shows extensive irregular areas of relatively mature-appearing fibrous tissue that was present within the septum as well as adjacent to and within the bundle of His. In other areas there were moderately fresh-appearing interstitial fibrosis and mononuclear inflammatory cells (Masson's trichrome stain).*

Comment

Since this was a retrospective study and neither viral cultures or serologic studies were routinely obtained at necropsy, little concrete data are available to substantiate or exclude viral infections. However, in the absence of positive bacterial cultures or known toxin exposure in all of the cases with histologic evidence of interstitial myocarditis, the best alternative explanation for the majority of myocardial findings is that of a viral infection of the myocardium.

Etiologic agents known to be responsible for myocarditis include bacteria, spirochetes, rickettsia, fungus, protozoa helmenthes, and viruses [*5*]. Viruses are most frequently implicated, but because the diagnosis is often not suspected until there has been a significant time delay, an exact diagnosis frequently cannot be made [*6*].

The most frequently reported viral agents which have been implicated in myocarditis are coxsackievirus A and B, influenza virus, echovirus, mumps virus, and rubella virus. Grist and Bell [*7*] reviewed 385 patients with suspected heart disease and determined that coxsackievirus B infections were associated with at least half of the acute cases of myocarditis. Burch et al [*8,9*] found evidence of coxsackievirus B antigen in the myocardium by immunofluorescent techniques in 30.9% of routine autopsy specimens and in 29 of 50 hearts of children examined at necropsy. Types B3 and B5 were identified most frequently.

Myocarditis is usually defined as an inflammatory lesion characterized by cellular infiltrates, usually predominantly mononuclear. The infiltrates are often present in the perivascular area. Lesions are focal or diffuse and may show predilection for subendocardial or subepicardial regions. Myocytolysis and necrosis are varied and are dependent on the agent involved. The subepicardial lesions are often associated with pericarditis. Lesions are usually not limited to the interstitium and muscle but may also involve specialized tissue such as the conduction system [*1,10–12*]. The location as well as the extent of the lesion will be the determinant of functional impairment or clinical manifestations [*10,11*].

Stevens et al [3] have defined myocarditis as a single focal inflammatory infiltrate of approximately 100 cells or more in the absence of ischemia. Lesions about half of that number are acceptable if many foci can be found within the myocardium. These rigid criteria may produce a false negative histologic diagnosis of myocarditis in some instances, particularly when only a few myocardial sections are available for study. Miranda et al [13], in their study of coxsackievirus B5 infection of mice, showed that despite a mortality rate of more than 50% at 4 weeks and approximately 70% at 12 weeks, the early histologic lesions in the hearts of these animals consisted of very small foci of cellular infiltrates and necrosis involving only two or three muscle fibers at 3 days after inoculation. Areas of necrosis increased in size and number but never involved more than 12 or 15 fibers. By 15 days after inoculation, the necrotic muscle was being resorbed, lesions were reduced in size, and fibrous tissue appeared. Similar findings in mice infected with coxsackievirus A and B have also been observed by Feinstone et al [14] and by Wilson et al [15].

More subtle myocardial changes are described by Jaskiewicz and Mrozinska [16] in acquired coxsackievirus B infection of mature female mice from their suckling mice infected by intraperitoneal injection of the virus. Gross changes were noted only in the mothers killed at 120 to 180 days after their progeny's infection. However, at 10 to 14 days after infection of the newborns, discrete, interstitial infiltrates were seen in the mothers' myocardium with homogenization of intensely acidophilic cytoplasm surrounding the neighborhood of the infiltrates. Later there was conglomeration of histocytes and fibrocytes in small areas. In some, the myocardial cytoplasm was acidophilic and homogenized. No calcific foci were noted. At 120 to 180 days, thin-walled dilated left ventricles were noted with proliferation of the left ventricular endocardial cells in association with subendocardial fibrosis.

The finding of left ventricular endocardial thickening with collagen and elastic fibers in the hearts of two patients is not surprising in light of several recent studies. This association of endocardial fibroelastosis and myocarditis has been demonstrated in several animal models and also by Hutchins in the human [15-19], which suggests that endocardial fibroelastosis can occur with or without significant interstitial fibrosis.

In all of the children who had definite histologic evidence of interstitial myocarditis none had gross evidence of chronic congestive heart failure at necropsy, and all but two had normal chamber size, valves, and ventricular wall thickness measurements. Although many had associated histologic evidence of inflammatory changes in other organs, the finding of focal inflammatory infiltrates or fibrosis in the heart, or both, cannot be discounted in the search for the pathogenesis of sudden death in the children reported here.

Of particular interest is that myocarditis was present in 15 of the 90 (17%) sudden, unexpected deaths and in only 2 of the 48 violent deaths examined (4%). These two groups, collected over a 3-year period, are not well matched for age, sex, or time of death and demonstrate the need for well-controlled prospective studies to validate the importance of these findings.

One cannot assume that death was the result of the myocarditis in all children who died suddenly and unexpectedly with the findings of an interstitial myocarditis. However, a 17% incidence of myocarditis in this group seems inordinately high and suggests that interstitial myocarditis is present much more frequently than commonly appreciated and may be the primary cause of death resulting from either a fatal arrythmia or cardiac failure secondary to myocardial dysfunction.

Arrythmias associated with myocarditis are not a rare event, but documentation of this occurrence as the final episode is not often reported for obvious reasons. Clinically, electrocardiographic evidence of myocarditis is very common and includes ST segment abnormalities, arrythmias, and ectopic beats secondary to atrial, ventricular, or intraventricular conduction defects [10,20-25].

Summary

This study suggests that the prevalence of "silent" myocarditis may be higher in the pediatric population than is generally suspected and may contribute to a significant number of sudden and unexpected deaths in children, particularly those older than one year of age. The incidence of histologic myocarditis in children dying a violent death is similar to that reported as an incidental finding in adults.

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C. M. Bandt, M.D.
Medical Examiners Office
Hennepin County Medical Center
5th St. and Portland Ave. South
Minneapolis, Minn. 55415