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A Cluster of Fulminant Myocarditis Cases in Children, Baltimore, Maryland, 1997

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Abstract. The true incidence of myocarditis in children is difficult to estimate because many mild cases go undetected. This study describes an unusual cluster of myocarditis cases that occurred in young children living in the greater Baltimore area between May and October 1997. A search of multiple comprehensive databases and interviews with area pediatric cardiologists were conducted to identify unreported cases and determine the background rate of myocarditis in the area. Seven cases of myocarditis were found as well as two with a similar clinical picture and myocardial fibrosis on tissue examination. Six case patients with active myocarditis and one child with fibrosis died. The case children were predominantly black (eight of nine) and male (seven of nine), with no identifiable risk factors. The disease was characterized by a fulminant course with malignant arrhythmias. The greatest number of pediatric myocarditis deaths reported in 1 year prior to 1997 was three. Myocardial tissues were examined using immunohistochemistry, *in situ* hybridization, and polymerase chain reaction but no etiologic agent was identified. This outbreak is unusual because of both the number of cases and the fulminant course of the disease in this group of children.

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Acute myocarditis is a disease of multiple etiologies, both infectious and noninfectious, characterized by inflammatory infiltrates in the myocardium. Many different infectious agents have been associated with acute myocarditis, but viruses (particularly enteroviruses) are thought to be the most common [5, 13] and typically produce a monocytic infiltrate [9]. Although sometimes reported in clusters during outbreaks of certain viral diseases, myocarditis is typically sporadic [6, 13]. The disease is often fulminant in neonates but presents less acutely and has an indolent course in toddlers and young children [13]. Viruses are difficult to culture from myocardial tissue, but recent advances in molecular diagnostics have allowed the demonstration of viral nucleic acid in both acute myocarditis and idiopathic dilated cardiomyopathy [7, 9, 11, 12], a disease thought to be a sequella of acute myocarditis in many cases [1, 9, 10].

In October 1997, several cases of myocarditis characterized by rapid deterioration and death occurred in the greater Baltimore area and were reported to the Centers for Disease Control and Prevention (CDC). An investigation was conducted to determine the cause of the illness, identify unreported cases, and determine the back-

ground rate of the disease. The results of the investigation are reported here, along with a summary of clinical and pathological findings.

Methods

Case Finding

An active search for cases of suspected myocarditis that occurred in infants and young children from January to October 1997 was conducted by interviewing Baltimore metropolitan area pediatric cardiologists; reviewing the medical records of seven major Baltimore metropolitan area hospitals; and examining the databases of the Maryland State Vital Statistics Office, the Hospital System Cost Review Commission (HSCRC), and the state chief medical examiner's office. The seven hospitals chosen for the medical records search were selected on the basis of (1) the presence of a pediatric cardiologist on staff, (2) a large number of pediatric inpatient admissions per year, or (3) evaluation and treatment of an identified case of myocarditis. To determine the background rate of myocarditis in the Baltimore metropolitan area, database searches for myocarditis cases were extended for the 2 to 5 years preceding 1997 (depending on the availability of information for each database). Database searches were conducted using *International Classification of Diseases* (9th revision, clinical modification) diagnostic codes for acute myocarditis (422), nonspecific myocarditis (429), cardiomyopathy (425), and Coxsackie myocarditis (074.2); the codes for conduction disorders (426), dysrhythmia (427), congestive heart failure (428), cardiomegaly (429.3), and cardiac arrest (427.5) were also included in the search of hospital records to increase the sensitivity of the search.

Medical records of any suspected case identified in the search were reviewed. The study population included children younger than 6 years of age who resided in the Baltimore metropolitan area. A probable case of myocarditis was defined as a compatible clinical illness (acute congestive heart failure or arrhythmia) and evidence of contractile dysfunction of the myocardium on echocardiography. A definite case of myocarditis was defined as a compatible clinical illness and histopathologic findings of a monocytic inflammatory infiltrate of the myocardium accompanied by necrosis and degeneration of myocytes on biopsy or autopsy. Children with congenital structural heart disease or identified diseases causing myocardial dysfunction were excluded.

Investigation of Recent Cases

Family members of every child with a probable or definite case that occurred between January and October 1997 were interviewed. Information was collected about early features of illness, the mother's prenatal and perinatal history, the past medical history of the case patient, and exposure of the infant to toxins, animals, or sick humans.

Laboratory Investigation

The results of routine and specialized laboratory investigations conducted by physicians who treated the case patients were reviewed and recorded.

Tissues from biopsies or autopsies were collected and shipped to the Enterovirus Laboratory, CDC, and Infectious Diseases Pathology Activity, CDC, for further analysis. Hematoxylin and eosin-stained tissues were reviewed and immunohistochemistry (IHC), and *in situ* hybridization (ISH) studies were performed. IHC assays were done using a two-step indirect immunoalkaline phosphatase technique. The primary antibodies used in the tests included two pools of antienterovirus antibodies that react against enterovirus 71, Coxsackie A and B viruses, and echoviruses (first pool: Coxsackie viruses B3–B6, and A9; second pool: Coxsackie virus B1 and echo viruses 7, 11, and 12), an antiadenovirus monoclonal antibody, and a polyclonal antimycoplasma antibody. Positive controls consisted of formalin fixed and paraffin embedded culture cells that had been infected with the different viral agents. Negative controls were the patient's tissues incubated with irrelevant antibodies.

ISH was performed in the same tissues by using a digoxigenin-labeled probe. This probe (5′ NTRE11E12) has been shown to detect enterovirus 71, Coxsackie viruses A7, A16, A21, and B1–B6, and echoviruses 7, 11, and 12 in formalin-fixed, paraffin-embedded infected cell cultures. Ribonucleic acid was extracted from heart muscle tissue from four of the seven case children and tested for enteroviruses by reverse transcriptase-polymerase chain reaction (RT-PCR) using primers that amplify all enterovirus serotypes [14]. Appropriate positive and negative controls were run in parallel with specimens for ISH and PCR.

Results

Seven cases of myocarditis (two probable and five definite) occurred among infants and young children in the Baltimore metropolitan area during 1997 (Table 1). Two more children were also identified with similar clinical illness but with myocardial fibrosis without acute inflammation on their tissue exam. The children with myocardial fibrosis were included in the subsequent investigation but are described separately. All case patients had onset of symptoms between May and October 1997.

For the years prior to 1997, review of the HSCRC database identified five discharges in children under the age of 6 years in 1993 for which myocarditis was listed as a diagnosis (two in 1994, one in 1995, and two in 1996) for the entire state of Maryland. Only one death was reported. It was not possible to identify individual patients in the HSCRC database to determine if each discharge represented a different patient. The medical records databases of the two hospitals with large pediatric cardiology groups recorded zero to two children with myocarditis per year for the years 1991 to 1996 (total both hospitals). The third Baltimore hospital with a pediatric cardiologist on staff reported no children with myocarditis prior to 1997. Search of the medical records of the four hospitals without a pediatric cardiologist on staff did not identify any cases in the previous 2 to 5 years. Because the diagnosis of myocarditis appeared on the hospital discharge record, it is likely that all the cases identified in the hospital record searches were also reported in the HSCRC database.

Case reporting in the vital statistics database and the state medical examiner's (SME) database overlapped such that myocarditis diagnoses made by the SME were also reported as cause of death in the vital statistics da-

Table 1. Demographic, clinical, and histologic features of pediatric myocarditis cases, Baltimore, Maryland, 1997

Case no.	Age (months)	Sex	Race[a]	Date of admission	Clinical presentation	Duration of prodrome (days)	Duration of CHF symptoms (days)	LOS (days)[b]	Outcome	Ventricular arrhythmia	Contractile dysfunction	Histology
1	7	f	b	5/4/97	Cough, rhinorrhea for 3 days, episode of lethargy, cold, blue extremities night before admission	3	<1	0	Died	nd[c]	nd[c]	Monocytic infiltrate
2	35	m	b	6/13/97	Intermittent vomiting and rapid/labored breathing for 2 or 3 days, but generally happy, playing	None	2–3	1	Died	No	Yes	Monocytic infiltrate
3	10	m	b	7/13/97	Incessant crying, stopped breathing	None	<1	0	Died	nd	nd	Monocytic infiltrate
4	4	m	b	8/6/97	Irritable, poor feeding, tachypneic	None	<1	1	Died	Yes	Yes	Monocytic infiltrate
6	5	m	b	9/20/97	Poor intake for 1 or 2 days, restless and limp, cyanotic spells × 3	None	1	15	Died	Yes	Yes	Monocytic infiltrate
7	14	m	b	10/10/97	Dyspnea	None	<1	3	Died	Yes	Yes	nd
8	0.5	f	b	5/16/97	Cough and sneeze for 4 days, choking and cyanosis on day of admission	4	<1	7	Alive	Yes	Yes	nd
					Case patients with fibrosis on tissue examination							
5	5	m	w	9/14/97	Poor intake for 4 weeks; sweating with feed Sept. 9, lethargic on Sept. 10, apneic spell Sept. 13	None	25	1	Died	Yes	Yes	Fibrosis
9	4	m	b	7/31/97	Approximately 2 months of intermittent tachypnea, decreased appetite	None	73	14	Alive	Yes	Yes	Fibrosis

m, male; f, female; b, black; w, white; nd, not done.
[a] Self-reported race.
[b] LOS represents time in days from presentation for evaluation and treatment to discharge or death.
[c] Test not done.

tabase. In addition, the vital statistics database also recorded postmortem diagnoses made by hospital pathologists in cases not sent to the SME. Three fatal cases were reported for the entire state in each of the years 1991–1993, two in 1994, and one per year in 1995 and 1996. Less than half of the case patients identified before 1997 lived in the Baltimore area and no predominant sexual or racial distribution was apparent.

Case Investigation

The affected children had a median age of 5 months (range 2 weeks to 2.9 years) (Table 1). Eight were black, and one was white. Seven were male, and two were female. The socioeconomic status of the children's families varied. Seven of the case children lived in Baltimore City and the other two in neighboring counties. There was no apparent clustering of case children by residence within the city. None of the case families had social contact with each other or knew of other children with myocarditis. Family size varied but was generally small. Six of the case children were from families with only one or two children, whereas three were from families with three or more children in the household. Only one child attended a day care. All nine case children had received routine, age-appropriate immunizations but none had received the same lot of vaccine for any immunization. No common risk factor or exposure was identified for the case children.

Clinical Features

All seven case children with myocardial inflammation and the two with myocardial fibrosis had been in good general health prior to the onset of symptoms related to their illness (Table 1). None of the case children had a history of a febrile illness or exanthem in the month prior to onset of myocarditis. One child (case patient 3) had had otitis media treated with antibiotics 4 weeks before the onset of myocarditis; however, all respiratory tract symptoms had resolved prior to myocarditis onset. Two children (case patients 1 and 8) had symptoms of an upper respiratory infection 3 or 4 days prior to the onset of myocarditis symptoms.

Six of the seven case children with myocardial inflammation died. Five of the seven fatal case children had rapid onset of signs and symptoms of congestive heart failure that occurred less than 24 hours prior to admission. A sixth fatal case child (case patient 2) experienced episodic shortness of breath for 2 or 3 days prior to his sudden collapse and death. On admission, four of the seven fatal case children had episodes of ventricular tachycardia, one developed electromechanical dissociation, and another had no rhythm at the time of his arrival at the emergency department. Five of the seven children were found to have contractile dysfunction of the myocardium documented on echocardiogram, and two of the seven died before echocardiography could be performed. Five of the seven fatal case children died within 24 hours of presentation to the hospital. The other two fatal case children (case patients 6 and 7) died 3 and 15 days after hospitalization, respectively, following intensive resuscitation and life-support measures, including extracorporeal membrane oxygenation.

One (case patient 8) of the seven case children with myocardial inflammation survived. The surviving case child was hospitalized at 2 weeks of age with a history of "gasping for air" and cyanosis for 1 day and remained in the hospital for 2 weeks. She had poor contractility noted on echocardiogram (ventricular shortening fraction of 23%) and transient ventricular tachycardia that responded to medical therapy. All symptoms of heart failure subsequently resolved and her cardiac function returned to near normal levels (ventricular shortening fraction of 30% at 6 weeks after discharge).

The two case patients with myocardial fibrosis had a more indolent clinical course prior to admission. Case patient 5 had a history of poor feeding and poor weight gain for 3 or 4 weeks, sweating while feeding for 5 days, and an apneic spell the day before admission. He was noted to have ventricular tachycardia at presentation to the emergency room and died soon afterwards. Case patient 9 had a history of an "abnormal breathing pattern" for 2 months before admission and developed more prominent signs of congestive heart failure, including diaphoresis with cool extremities, a few days before admission. This child was hospitalized for 15 days and spent most of the time in the intensive care unit. He was subsequently discharged but had persistent myocardial dysfunction as determined by echocardiogram. Organic acids and carnitine levels were normal, and toxicology was negative.

Etiologic Investigation

Two case children had amino acid and organic acid levels measured, and two others had carnitine levels measured; all were normal. In addition, toxicologic studies were done on one child in the hospital and three others at autopsy; all were negative for drugs and alcohol. Serum specimens from three children were tested for antibodies to adenoviruses and Coxsackie viruses, two were tested for influenza and Epstein–Barr virus, and one was tested for human immunodeficiency virus and toxoplasma; all were negative. Four children had viral cultures of stool or nasopharynx; one nasopharynx specimen (from case patient 8) was positive for human parainfluenza virus type 3. All other specimens were negative.

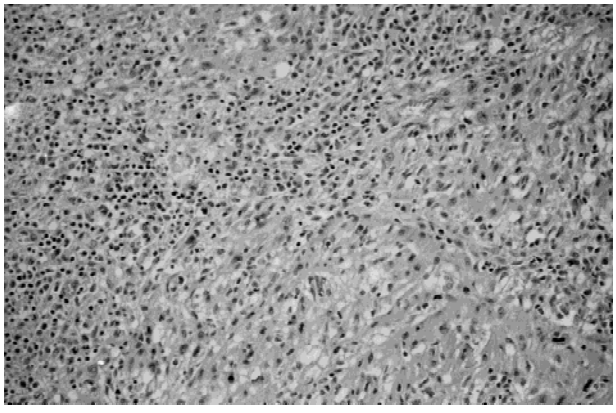

Fig. 1. Hematoxylin and eosin stain of the heart of case 4 showing marked inflammatory infiltrate composed of mononuclear cells and eosinophils. The myocytes show severe degeneration as demonstrated by vacuolization, pycnotic nuclei, and eosinophilic cytoplasm (magnification ×200).

Table 2. Results of tissue testing for etiologic agent (CDC)

Case no.	EV PCR[a]	EV *in situ*[b]	EV IHC[c]	Ad IHC[d]	Myc. IHC[e]
1	Negative	Negative	Negative	Negative	Negative
2	nd	Negative	Negative	Negative	Negative
3	Negative	Negative	Negative	Negative	Negative
4	Negative	Negative	Negative	Negative	Negative
5	nd	Negative	Negative	Negative	Negative
6	Negative	Negative	Negative	Negative	Negative
9	nd	Negative	Negative	Negative	nd

nd, not done.
[a] Polymerase chain reaction study for enterovirus.
[b] *In situ* hybridization test for enterovirus using a probe which detects enterovirus 71, A7, A16, A21 Coxsackie B1–B6, and echo viruses 7, 11, and 12.
[c] Immunohistochemistry for enterovirus using two sets of pooled enterovirus antibodies. Case 6 showed faint immunoreactivity.
[d] Immunohistochemistry for adenovirus.
[e] Myocoplasma immunohistochemistry.

Tissue Studies

Tissue specimens were available from seven of the nine children—six from autopsy specimens and one biopsy from a child that survived. On histopathological examination of the heart, five of the six fatal case children had myocarditis, as evidenced by marked monocytic infiltrate of the myocardium accompanied by myocyte degeneration and necrosis (Fig. 1). Histological examination of tissue from case patients 5 and 9 demonstrated myocardial tissue fibrosis without active inflammation. IHC and ISH tests for adenoviruses, enteroviruses, and mycoplasma were negative on heart tissue specimens from all seven case children from whom tissues were available (Table 2). PCR for enteroviruses was also negative in four case patients from whom sufficient tissues were available.

Discussion

These results confirm that an increased number of myocarditis cases occurred among children younger than 6 years of age in the Baltimore metropolitan area between May and October 1997. Reviews of several databases indicated that the entire state of Maryland typically has fewer than four cases of myocarditis in children under 6 years of age each year. It is possible that a similar increase may have occurred in 1993 if each of the discharges reported in the HSCRC database represent a unique individual. Although the precise number of cases of any nonreportable illness is always difficult to determine, it is likely that we identified all the pediatric myocarditis cases diagnosed in the Baltimore area in 1997. Myocarditis cases are likely to be diagnosed by, or referred to, a pediatric cardiologist if the diagnosis is made premorbidly or by the SME in the event of sudden unexplained death.

These cases were remarkable for their unusually fulminant course and high mortality in an age group in which the disease is typically indolent and for the striking predominance of black males in the group. The disease was distinguished by a sudden onset and rapid progression to a fatal outcome, often associated with malignant ventricular arrhythmias, and the absence of prodromal illness. The outbreak was unusual in that it did not coincide with any recognized outbreak of viral illness in the community. Unfortunately, we were not able to identify a specific agent responsible for this outbreak; however, the histopathological findings of a monocytic myocarditis and the spring, summer, and fall occurrence implicate a viral agent as the most likely cause. Inability to identify a single agent is not an uncommon result of myocarditis outbreak investigations. Although enteroviruses, in particular group B Coxsackie viruses, are considered to be the most common cause of viral myocarditis, viruses are often difficult to isolate from myocardial tissue specimens [2, 8, 9].

Two children with myocardial fibrosis had a more indolent course than those with inflammatory infiltrates. Although the cause of a dilated cardiomyopathy is often unknown, it is clear that acute myocarditis can progress to a chronic, fibrotic stage [1, 9, 10] and that viral RNA can occasionally be demonstrated in the myocardium of patients with cardiomyopathy [7, 9, 11, 12]. There were no features of the medical history or the histopathological appearance of the tissues of the children with fibrosis to suggest either congenital heart disease or other noninfectious causes of cardiomyopathy.

Our investigation reported here clearly demonstrates

that an outbreak of myocarditis occurred in Baltimore in 1997. However, despite our best efforts, we were unable to discover the cause. Prevention of future outbreaks will be possible only when the etiology of this disease is better understood. We hope that our report will help in this process by raising the level of awareness for the need of vigilance for future outbreaks, improved case reporting, and further refinement of diagnostic tools.

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