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Recurrent Pericarditis in Children and Adolescents

Report of 15 Cases

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OBJECTIVES The aim of this study was to analyze the clinical findings, course, and treatment of recurrent pericarditis (RP) in patients with onset in childhood and adolescence.

BACKGROUND Recurrent pericarditis is a chronic condition that has presented problems in management. Knowledge about this disease is based on observations in adults, and no series of children has previously been published.

METHODS Fifteen children (nine males, six females) in whom pericarditis had recurred at least twice were encountered in the period 1985 to 1998. Their age at onset was 6.5 to 16.8 years (mean 11.6 years), and the follow-up was 4.0 to 16.2 years (mean 8.0 years).

RESULTS Recurrent pericarditis was preceded by open-heart surgery by 1 month to 5 years earlier in 7 of 15 patients. The six children with an atrial septal defect (ASD) had an operation at an older age (mean 9.9 years) than usual (mean 4.8 years). The risk of RP in children operated on for ASD at the age of six years or later was 5%. An initial attack of pericarditis was associated with pleuritis and/or pneumonia in 10 of 15 patients and with colitis in 2 of 15 patients During follow-up, the patients had 2 to 30 recurrences (mean 9.9). Later attacks tended to be milder. At the end of follow-up, 7 patients had been without attacks for ≥4 years, whereas after 4 to 16 years, the remaining patients still had active disease. No instance of constriction was found. Altogether, 11 of 15 patients were treated with corticosteroids. However, corticosteroids, whether alone or with methotrexate (n = 5), azathioprine (n = 1), cyclosporine (n = 1), or colchicine (n = 4) did not prevent recurrences.

CONCLUSIONS The most frequent background for RP in children was the closure of ASD after the age of six years. Its course was unpredictable and often chronic, irrespective of the underlying cause or the therapy given. Colchicine did not prevent relapses. (J Am Coll Cardiol 2003;42: 759–64) © 2003 by the American College of Cardiology Foundation

Recurrences develop in up to 15% to 30% of adult patients with acute pericarditis (1). Recurrent pericarditis (RP) may be a debilitating disease resistant to therapeutic interventions (1–6). The etiology of the initial attack, and especially the cause of recurrences, often remain unclear. Some cases are connected with chronic inflammatory diseases, and others are preceded by cardiac operation (2), but the pericarditis often seems to be idiopathic. Only single children with RP have been described (3–8). We report the clinical findings and follow-up data of 15 children and adolescents with RP.

METHODS

Patients. This report is based on a retrospective analysis of 15 patients (9 males, 6 females) seen during 1985 to 1998 (Table 1). Their age at the onset of the disease was 6.5 to 16.8 years (mean 11.6 years), and the follow-up time was 4.0 to 16.2 years (mean 8.0 years). Eleven of them were followed up at the Hospital for Children and Adolescents, Helsinki.

The initial diagnosis of pericarditis was based on pericardial pain and increased pericardial fluid documented by echocardiography. Patients were included in our series if the pericarditis had relapsed at least twice after the initial attack. Pain and increased pericardial fluid documented recurrences, but, in case of several recurrences, diagnoses of last recurrences were based on typical pain only. The criterion for a relapse was recurrence of characteristic symptoms and findings after a period of at least one month since the onset of the previous attack. Patients with verified systemic connective tissue diseases were excluded.

We analyzed the following aspects of the disease in the patients' records: features of the pericarditis during the initial attack, number and features of recurrences, clinical findings, and therapy given. Preceding events such as cardiac operations and concurrent diseases were recorded. A comparison was made between postoperative patients and others and between corticosteroid-treated patients and others.

RESULTS

Clinical findings. INITIAL EPISODE. At presentation, 12 children were febrile, and 10 were seriously ill. All had pericardial pain, mostly in the chest, but also in the shoulder, back, abdomen, or neck. The average diastolic thickness of pericardial fluid was 8.3 mm, and one patient

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Abbreviations and Acronyms

ASD = atrial septal defect
CRP = C-reactive protein
NSAID = nonsteroidal anti-inflammatory drug
RP = recurrent pericarditis

had mild tamponade. The chest X-ray showed cardiac enlargement in 14 patients and pleuritis and/or pneumonia in 10 patients. The electrocardiogram was normal in 3 patients, showed either short-lasting T-wave or ST-segment changes in 10 patients and low-voltage QRS complexes in 1 patient. Increased serum creatine kinase-MB levels were found in three children. The erythrocyte sedimentation rate and C-reactive protein (CRP) values were clearly elevated (Table 2), except in one patient who had massive polyserositis.

RECURRENCES. In total, 15 patients had 149 recurrences (mean 9.9, range 2 to 30) during follow-up (Table 1, Fig. 1). The principal symptom during recurrences was pain, similar to that during the initial attack. In only four patients was pleuritis/pneumonia observed during recurrences. In general, with increasing time, recurrences became less severe and the interval between attacks became prolonged. This tendency to a milder course was also seen in cardiologic and laboratory findings, as summarized in Table 2. In two patients (Patients #3 and #7), however, clinically mild recurrences gradually developed into monthly episodes of pericarditis, and in two patients (Patients #5 and #8), recurrences regained the initial intensity. None of the recurrences resulted in tamponade or constrictive pericarditis.

The longest quiescence between attacks was 1 to 11 months (n = 6) or 12 to 27 months (n = 9). So far, seven patients have been without further attacks for more than four years, and these patients may probably be regarded as cured of RP (Figs. 1 and 2). In this group, active disease, calculated from the initial attack to the onset of the last recurrence, lasted from 0.5 to 3.5 years (mean 1.9 years), and they have been followed up for 4.0 to 11.1 years (mean 6.8 years) after the last recurrence. For those quiescent for <4 years, the active disease has varied from 3.2 to 15.5 years (mean 6.7 years).

PERICARDIAL FLUID AND HISTOPATHOLOGY. In three patients, pericardial puncture or drainage was done during the initial attack and in four during a recurrence without complications. Pericardial fluid was clear on four occasions, slightly cloudy once, and slightly bloody twice. Its protein content was 48 g/l (measured once). The white cell count varied from 11.4 to 19.5 $\times 10^9$/l (60% to 88% polymorphonuclear cells and 12% to 40% mononuclear cells), corresponding to the white cell findings in the blood. In all samples, bacterial, tuberculous, and fungal cultures were negative. Viral isolation yielded herpes simplex type 1 in one sample; however, there was no increase in the viral antibody titer. Pericardial biopsy displayed fibrosis and nonspecific inflammation in two patients. Pericardiectomy was not performed in any of the patients.

Preceding and associated conditions. OPEN-HEART SURGERY. Open-heart surgery preceded RP in 7 (47%) of 15 patients. An operation was performed for an atrial septal defect (ASD) in six patients and a ventricular septal defect in one patient (Table 1). The proportion of ASD patients (86%) among our postoperative patients with RP was 10 times higher than the 8.4% proportion of ASD operations among Finnish pediatric cardiac operations in general (9). Also, the average age at the ASD operation (9.9 years [range 6.3 to 15.7 years]) was higher than that at all ASD operations (4.8 years) in Finland during the same period.

Table 1. Basic Data on the 15 Patients With Recurrent Pericarditis

Patient No.	Gender	Age at Initial Attack (yrs)	Number of Relapses	Type of Heart Defect	Postoperative Interval to Pericarditis (months)	Associated Conditions During Initial Attack
1	M	16.8	4	ASD	59	Pleuritis, scar irradiation, Rubinstein Taybi syndrome
2	F	10.8	6	VSD	1	
3	M	8.4	30	ASD	7	Pneumonia, scarlatina
4	F	10.0	9	ASD	2	Pleuropneumonia
5	M	9.4	13	ASD	22	Pleuropneumonia, appendicectomy
6	M	6.5	2	ASD	3	
7	F	15.8	26	ASD	3	
8	M	15.5	14			
9	M	12.5	10			Pneumonia
10	F	7.5	2			Pleuritis, ascites, thyroiditis
11	M	10.7	2			
12	F	6.9	5			Pleuritis, colitis, mesalamine
13	M	15.0	15			Pleuritis
14	M	13.1	5			Pleuropneumonia
15	F	15.4	6			Pleuropneumonia, colitis, erythema-nodosum, Noonan's syndrome

ASD = atrial septal defect; VSD = ventricular septal defect.

Table 2. Clinical Findings During Initial Attack of Pericarditis and Recurrences

Pericarditis	No. of Attacks	Fever (% of Attacks)	ESR (mm/h)*	CRP (mg/l)*	ECG Changes (Changes/No. of Attacks Studied)	Pericardial Effusion (Effusion/No. of Attacks Studied)
Initial attack	15	80	60 (10–96)	150 (12–307)	77% (10/13)	100% (15/15)
Relapses 1–3	42	62	62 (4–120)	134 (10–340)	73% (19/26)	89% (34/38)
Relapses 4–6	32	50	46 (13–97)	71 (10–270)	42% (8/19)	59% (16/27)
Relapses 7–9	21	19	17 (7–47)	44 (10–153)	44% (4/9)	43% (3/7)
Relapses 10–15	28	7	39 (7–90)	104 (10–260)	50% (4/8)	42% (5/12)

*Data are presented as the mean value (range).
CRP = C-reactive protein; ECG = electrocardiographic; ESR = erythrocyte sedimentation rate.

Calculated from the total number of ASD operations performed during the study period, the risk of RP was 1.6% and in those who had an operation at the age of six years or older, 5%. Also, the patient with a ventricular septal defect was operated on at an older age (9.8 years) than is usual. Recurrent pericarditis appeared within two years after cardiac surgery in six children (Table 1). In the patient with an interval of five years, pericarditis was triggered by radiation of the keloid thoracotomy scar.

OTHER ASSOCIATED CONDITIONS. The initial attack of pericarditis was associated with colitis in two children (Table 1). The disease was of short duration in one patient (Patient #15), and in the other (Patient #12), ulcerative colitis was treated with prednisolone and mesalamine. She had five recurrences of pericarditis, but none after mesalamine was discontinued. Patient #10 presented with polyserositis and autoimmune thyroiditis and had a high titer of antinuclear antibodies, but no definable connective tissue disease has appeared during follow-up. We aimed at exclusion of connective tissue diseases by immunologic studies. Antinuclear antibodies were increased in 1 of 14 patients (Patient #10). Antibodies to extractable nuclear antigen and to double-stranded deoxyribonucleic acid were both normal in eight patients studied, as well as rheumatoid factor in five patients. Serum immunoglobulin levels (n = 9) and complement components C3 and C4 (n = 11) were normal or increased. However, a family history revealed systemic lupus erythematosus in two families and HLA B27-positive spondyloarthropathy with carditis in one. The sister of Patient #10 had autoimmune thyroiditis. The grandfather of Patient #14 had had several episodes of pericarditis of unknown etiology.

INFECTIONS IN ASSOCIATION OF THE INITIAL ATTACK AND RECURRENCES. No microbiologic etiology could be established for pleuritis or pneumonia found in 10 of 15 patients during the initial attack. Blood cultures were obtained in 11 of 15 patients with negative results. Signs of upper respiratory tract infection were noted at presentation in four patients, one of whom had had scarlatina and another had undergone an appendectomy before the initial attack. Antibiotic treatment was administered to nine patients.

Upper respiratory tract infections were recorded in 29 recurrences of 9 patients. An attempt to specify the etiology of these infections was done only occasionally: influenza A,

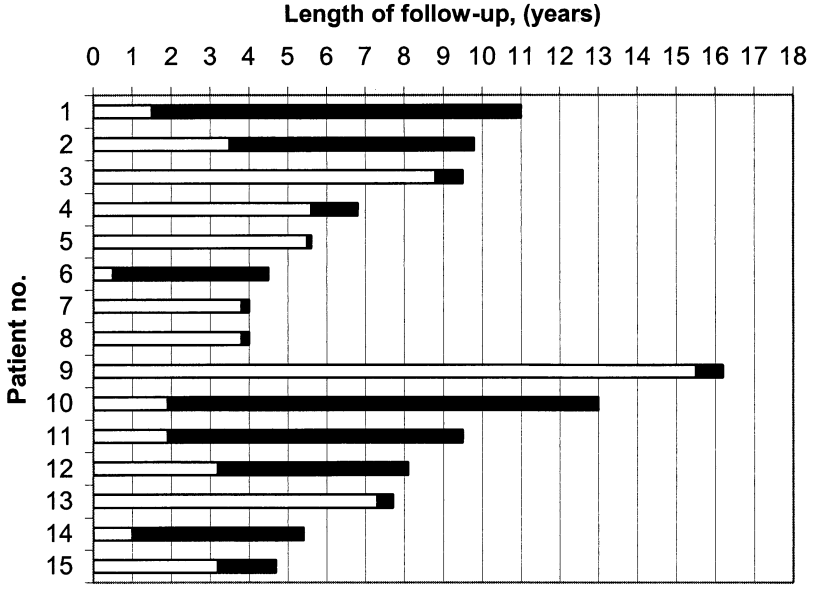

Figure 1. Follow-up times in each of the 15 patients. The **open part of the bar** shows the duration of active disease, and the **solid part** shows the follow-up time after the last recurrence. Patient numbers correspond to those in Table 1.

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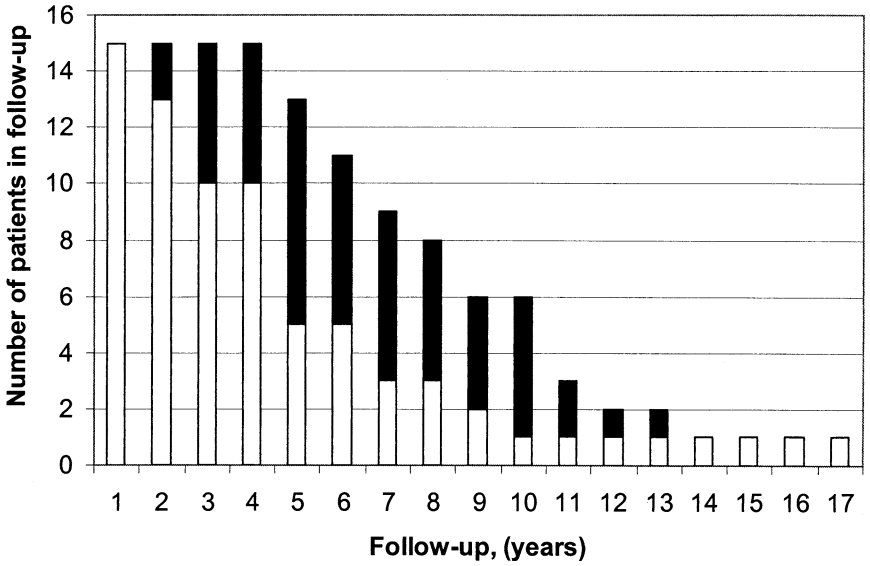

Figure 2. Total number of patients **(whole bar)** and patients with active disease **(open part of bar)** in each follow-up year.

influenza B, adenovirus, parainfluenza 2, and *Mycoplasma pneumoniae* infection were all diagnosed once. Interestingly, Patient #8 had two relapses triggered by influenza vaccination. In contrast to the initial pericardial attack, pleural effusion or pulmonary infiltrate was seen only during nine recurrences. Most recurrences did not have any obvious triggering factor.

Comparison between postoperative and other cases. There were no obvious differences in the nature or course of RP between patients who had an operation for heart disease and other patients. During the 4-year follow-up of all patients, the number of recurrences was comparable in the operated patients (mean 8.1 [range 2 to 26]) and the others (mean 7.3 [range 2 to 14]). During the initial attack, CRP was 67 to 307 mg/l (mean 153 mg/l) in the operated patients and 12 to 295 mg/l (mean 146 mg/l) in the others. Three of seven postoperative patients and four of eight other patients were apparently cured of RP during follow-up.

Drug therapy. Four patients (Patients #1, #4, #6, and #9) were treated with nonsteroidal anti-inflammatory drugs (NSAIDs) only. The remaining 11 patients received corticosteroids, seven of them even during the initial attack. In two patients, predniso(lo)ne was given as one- to two-week courses. Long-term (more than two years) prednisolone, mostly on alternate days, was given to four patients, and in the rest, the regimen varied. Initially, CRP was 12 to 295 mg/l (mean 135 mg/l) in the group treated with corticosteroids and 96 to 307 mg/l (mean 201 mg/l) in the others, suggesting that the initial attack may not have been less severe in the group receiving no corticosteroids. During a follow-up period of 4 years, available in all patients, the number of recurrences was 2 to 26 (mean 8.3) in the group treated with corticosteroids and 2 to 6 (mean 4.5) in those not so treated. Remission of at least 4 years was achieved by 5 of 11 patients of the former group and 2 of 4 of the latter group. Peroral methotrexate 10 to 15 mg/week in 4 patients and 25 mg intramuscularly in 1 patient did not prevent recurrences, neither did azathioprine 100 mg/day in 1 patient. One child (Patient #14) was receiving cyclosporine A for 9 months and had two more recurrences during that time, but has since been off treatment and well for 4.5 years.

Colchicine 0.5 to 2.0 mg/day was given to 4 patients (Patients #3, #5, #7, and #8) who had relapsed despite corticosteroid treatment. However, these patients had 3 to 10 recurrences (mean 5.8) during a period of 6 to 27 months (mean 13.3 months) on colchicine. Before colchicine treatment these patients had 4 to 15 attacks (mean 7.5) during a period of 10 to 71 months (mean 35 months).

DISCUSSION

Open-heart surgery as a background factor. Cardiac surgery preceded RP in 47% of our patients, in contrast to the findings in adult series where the proportion of postoperative cases varied from 13% (3) to 25% (10). The incidence of post-pericardiotomy syndrome is higher in children than in adults (11), which may explain the difference. On the other hand, post-pericardiotomy syndrome occurs far more often in older children than in infants (12). In accordance, all seven postoperative patients had an operation at an older age than is usual for their defects. The Registry for Cardiac Operations in Finnish Children allowed us to calculate the risk of RP after ASD operation. An unexpectedly high 5% risk was found among children operated on after the age of six years. Altogether, RP seems to be a disease affecting principally older children and adolescents. The clinical picture, course, and prognosis of RP were similar in the postoperative and other patients, indicating that the character of the trigger is not of importance for the subsequent nature of the disease.

Associated conditions at the time of initial pericarditis. Pneumonic infiltration or pleural effusion found in 67% of our patients may reflect the same immune-mediated process that inflamed the adjacent pericardium, as no microbiologic etiology could be verified. In fact, pleuritis is an essential feature in post-pericardiotomy syndrome (2). Pleuritis and/or pulmonary infiltration were found both in operated and nonoperated patients, reflecting the similar pathophysiologic mechanism of RP. Two patients had inflammatory bowel disease, in which pericarditis may very rarely occur as an extraintestinal manifestation (7). In one of these patients, both the initial attack and the recurrences of pericarditis were clearly associated with mesalamine treatment. This observation stresses the causal role of 5-aminosalicylic acid compounds in pericarditis, believed to be due to type IV hypersensitivity reaction, as discussed in detail by Sentongo and Piccoli (7).

Triggers of recurrences. Clinical documentation of respiratory tract infections was found in patient records in 20% of all relapses. *Mycoplasma* infection is among the infections reported to cause RP (13), but appropriate antibiotic treatment did not prevent further recurrences in our patient. Interestingly, one patient had relapses repeatedly after influenza vaccinations, as described previously in an adult (14). Thus, if pericarditis occurs after influenza vaccination, further influenza vaccinations should be avoided. It can be speculated that epi-pericardial injury due to any of a variety of insults may initiate an autoimmune process, which is reactivated by microbe-induced immune stimulation. Persistent T-cell activation may be induced by antigens intrinsic to the epi-pericardium and cross react with viral antigens because of molecular mimicry. Coxsackie adenovirus receptors and co-receptors have been described on cardiac cell surfaces (15).

Genetic factors. Genetic factors may contribute to the propensity to recurrences in pericarditis. Familial clustering of RP has recently been described (16), and the grandfather of one of our patients had RP. The clinical picture of RP shares features of hereditary recurrent inflammatory disorders, which are characterized by repeated attacks of fever and organ-localized inflammation affecting mainly the abdomen, musculoskeletal system, and skin. In a recent series of 394 patients with recurrent inflammatory syndrome, 2 patients had RP as the only sign of the disease (17).

Treatment. Controlling chest pain and pericardial effusion during the attacks and preventing recurrences are the main goals of therapy. We found no harm in our practice not to restrict the physical activity of patients between the attacks when clinical findings were normal. The NSAIDs are the commonly used first-choice treatment, but the response is often unsatisfactory, and most patients (11 of 15 in our series) receive corticosteroids (1,4). Corticosteroids effectively suppress pericardial pain and inflammation during acute attacks. However, the efficacy of corticosteroids in preventing relapses has been questioned, and warnings have been issued about steroid dependence (6,10). Recurrences occurred in our patients on corticosteroids, and, in fact, the mean number of relapses in steroid-treated patients was nearly twice that of those not so treated. Because of systemic side effects, steroids were discontinued in two patients. The subsequent relapses were not more frequent and were successfully treated with NSAIDs only. As the disease gradually tends to quiet down, it seems possible to avoid corticosteroids during the later recurrences, even in patients who initially required them because of intractable symptoms. This is especially important in patients with frequent late recurrences and/or those at risk of steroid dependence, but without clear-cut evidence of active inflammation, such as an elevated CRP value. Although the mechanism of pain in such cases is unknown (possibly due to low-grade inflammation or so-called complex regional pain syndrome [18]), pain should be treated with NSAIDs or pain killers only. None of the other immunosuppressive drugs given to seven patients prevented recurrences. Thus, we recommend treatment of children with RP primarily with NSAIDs and the use of corticosteroids only in those with severe symptoms and only temporarily, if possible. As RP is uncommon, its treatment is challenging. In addition, there is a risk of steroid dependence, so patients should be followed in centers familiar with this disease.

Colchicine. Colchicine has recently been used in RP, with good results in adults and subsequently in children (8,10), and it has been recommended as the drug of choice in this disease. In a international multicenter study, 51 patients were treated with colchicine and only 7 patients (13.7%) presented with new recurrences (10). Our experience is in contrast to that study, as the response in all our four patients was unsatisfactory. Colchicine is an effective drug in familial Mediterranean fever, a disease prevalent in countries where good results with colchicine have been obtained in RP. Mediterranean fever has not been observed in the Finnish population. The effectiveness of colchicine in RP has not been tested in a double-blind, controlled manner. This would be important because of the unpredictable natural course of RP and the tendency of recurrences to settle down (Fig. 2).

Prognosis. The course of RP was often long and unpredictable, irrespective of the cause or triggering event. However, the activity of the disease seems to "burn out" gradually (Figs. 1 and 2), independent of the type of drug treatment used. In 7 of 15 patients, remission has lasted for over 4 years. The prognosis of RP may thus be somewhat better in children than in adults, as only 9 of 31 patients followed by Fowler and Harbin (3) stayed in remission for 2 years or more. Mild tamponade was found only in one child. No instance of constriction appeared.

Study limitations. Recurrent pericarditis is an uncommon disease in children. The 15 cases of this series were encountered during a 14-year-long period. Therefore, only a retrospective analysis of the patients was possible.

Conclusions. The most frequent background for RP in children was the closure of ASD after the age of six years.

The course of RP was unpredictable and often chronic, irrespective of the underlying cause and therapy given. Colchicine or other immunosuppressive drugs did not prevent relapses. Therefore, we prefer the use of NSAIDs in the treatment of RP in children.

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