Review

New insights in the pathogenesis and therapy of idiopathic recurrent pericarditis in children

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ABSTRACT

Pericarditis has several different causes, however, in about 70% of paediatric patients, a specific aetiology cannot be detected and the pericarditis is considered idiopathic. Recurrences may occur in up to 15–30% of cases. The pathogenesis of recurrent disease is controversial. Infectious, autoimmune and autoinflammatory pathways have been proposed as mechanisms involved in recurrences. Therapeutic strategies are not standardised, non-steroidal anti-inflammatory drugs at high dosages being the mainstay of therapy with the possible addition of low dose colchicine to prevent recurrences. Biological agents are considered a possible new therapeutic frontiers in the care of idiopathic recurrent pericarditis.

Introduction

Pericarditis is an inflammation of the pericardium (1) that accounts for about 5% of all children who present with chest pain to a paediatric emergency department (2).

Acute pericarditis is defined as at least 2 of the following criteria: typical chest pain (sharp and pleuritic, improved by sitting up and leaning forward), pericardial friction rub, suggestive ECG changes (widespread ST elevation or PR depression), new or worsening pericardial effusion (3-5). Recurrent pericarditis (RP) is defined by recurrent chest pain and one or more of the following signs: pericardial friction rub, ECG changes, echocardiographic evidence of pericardial effusion, and elevations in the white blood cell count or erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) (3-5).

Pericarditis has a vast array of causes that can be separated into infectious and non-infectious categories (1, 6). Viral infection is the most frequent probable or identifiable cause of pericarditis in children. In most cases, patients report a 10- to 14-day prodrome of respiratory or gastrointestinal illness. Echovirus, Cocksackievirus, Influenza virus, Epstein-Barr virus and Parvovirus B19 are often responsible for viral pericarditis (7).

Bacterial pathogens are implicated in only about 5% of cases (6, 8, 9). Primary purulent pericarditis is usually the result of haematogenous bacterial spreading to the pericardium from another site or by extension from adjacent organs (10). *Staphylococcus aureus* and *Haemophilus influenzae* are the most frequently involved bacteria. Tuberculous pericarditis is rare and mainly present in countries where tuberculosis is endemic or in immunocompromised patients (6, 7).

Non-infectious pericarditis can be associated to immunoreactive causes such as juvenile idiopathic arthritis (JIA), systemic lupus erythematous, Sjögren's syndrome, rheumatic fever, postpericardiotomy syndrome, metabolic diseases, traumatic and neoplastic causes (Hodgkin's disease, lymphoma and leukaemia) (6, 10-12). Radiation therapy may affect all layers of the heart, especially after mediastinal or breast irradiation (12). Pericarditis has also been reported as a complication of open-heart surgery (13).

An emerging cause of pericarditis is represented by auto-inflammatory diseases that include familial Mediterranean fever (FMF) and tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) (14).

Acute pericarditis is characterised by progressive, frequently severe, chest pain that tends to be substernal, sharp and worse with inspiration; a pericardial friction rub is pathognomonic but is not common (20% of cases) (5). Electrocar-

diography may show widespread ST-segment elevation and/or PR depression in most cases. Echocardiography may be normal or may reveal a pericardial effusion in approximately 60% of cases (6), usually mild. Chest radiography is frequently negative, but cardiomegaly can be seen in patients who have a substantial pericardial effusion. In one third of patients a pleural effusion may be detected in the first attacks (15). Plasma troponin I may be raised reflecting myocardial involvement (16); leukocytosis, increased CRP and ESR are common findings (5, 15, 17).

Extensive laboratory examinations and imaging investigations are not necessary in the majority of patients, but may be required when severe disease course or concomitant symptoms might rise the suspicion of neoplastic, tuberculous or purulent pericarditis (1). Computerised tomography and magnetic resonance imaging provide excellent visualisation of the pericardium, including areas not visualised by echocardiography (9). Positron emission computed tomography can be a useful supplement to other imaging modalities and maybe helpful in distinguishing an infectious or malignant process from an inflammatory process (18).

Pericardiocentesis is indicated for pericardial effusion with clinical tamponade, purulent pericarditis, a high suspicion of tumour and if diagnosis needs clarification (9). If clinically appropriate, diagnostic tests may include tuberculin skin test and QuantiFERON-TB test (3).

In up to 68% of paediatric patients (19) and in more than 80% of adult cases (6, 15, 17), however, a specific aetiology cannot be detected and pericarditis is considered idiopathic; in these patients recurrences after the initial attack are frequent and may occur in about 15–30% of children (13) and 20–50% of adults (4, 17).

The pathogenesis of idiopathic recurrent pericarditis (IRP) remains controversial but is presumed to be related to autoimmune mechanisms in the majority of cases. Suggested explanations of recurrences include: insufficient dose and/or duration of non-steroidal anti-inflammatory drugs (NSAIDs), early corticosteroid treatment causing increased viral replication in pericardial tissue, too rapid tapering of corticosteroids, re-infection and exacerbation of the connective tissue disease (3, 8, 12). In Table I all paediatric patients with IRP described in the English medical literature are summarised.

Treatment strategies of IRP are not standardised and, therefore, the choice of the most appropriate treatment is difficult, also because of the lack of randomised trials to guide therapy (3, 20, 21).

In this review, we will discuss the pathogenesis of recurrent pericarditis in children and new possible strategies of treatment.

New hypotheses about the pathogenesis of IRP: the role of autoimmunity and autoinflammation

RP is generally idiopathic or the complication of a post cardiac injury and it is often a frustrating disease for both patients and physicians given the absence of standardised therapies (8). The pathogenesis of the disease is often unclear; however, it shares some characteristics with autoimmune and autoinflammatory diseases.

In a report examining 15 cases of IRP in children and adolescents, Raatikka *et al*. found that the most frequent cause of IRP was open-heart surgery (13). The authors reported that open-heart surgery preceded RP in 7 (47%) of 15 patients included in the study, in contrast with the findings of the adult series where the proportion of postoperative cases varied from 13% to 25% (15, 22, 23).

Autoimmune damage involving the pericardium is often suspected in IRP given the presence of pro-inflammatory cytokines (IL-6, IL-8, IFN-gamma) in pericardial fluid (24), the presence of antinuclear autoantibodies (ANA) in the sera of many patients (11), the occurrence of new autoimmune diagnoses (11), and a good response to anti-inflammatory or immunosuppressive therapy (20, 25-27).

Dalla Pozza *et al*. (28) detected the presence of antimyolemmal antibodies (AMLAs) in four paediatric patients with higher inflammatory activity and recurrent pericarditis. AMLAs are auto-antibodies detected by the indirect immunofluorescence technique and directed against myocardial tissue (28, 29). These antibodies have been shown to play a role in the pathogenesis of perimyocarditis (29) and to be a prognostic indicator of disease severity in myo- and perimyocarditis in adults (30). A prolonged persistence of IgM-type AMLAs was found in the sera of 3 paediatric patients: two of them presented acute inflammation as the initial event and one with 48 recurrences during 5.5 years. The fourth patient showed a fast conversion from IgM to IgG-type AMLAs after a less acute initial presentation and suffered 4 mild recurrences during a 48-month follow-up. Consequently, the authors suggested searching for AMLAs in all children with unexplained recurrent pericarditis. Paediatric patients with a persistence of IgM-type AMLAs may face frequent recurrences and should be monitored closely (28).

In a study carried out on adult patients, anti-heart or anti-intercalated disk autoantibodies were found in 67.5% patients with IRP (31).

ANA have been detected in 43.4% of adult patients with IRP and in only 9.8% of healthy controls ($p<0.001$). Low titers (1/40–1/80) have been found in 37.7% of patients, while a moderate positivity (1/160–1/320) can be detected in 7.7 % of patients with IRP (11).

Taken together, these data suggest that, in at least a group of patients, the disease may have an autoimmune origin.

IRP also shares many features with autoinflammatory diseases. The autoinflammatory syndromes are a group of genetically different but clinically similar conditions characterised by recurrent attacks of fever, rash, serositis, lymphadenopathy and musculoskeletal involvement. FMF, hyperimmunoglobulin D syndrome, TRAPS and the cryopyrin-associated periodic syndromes (CAPS) are included in this category, where genetic mutations lead to dysregulation of the innate immune system and to episodic manifestations of systemic inflammation. Nearly all mutations that have been linked to the autoinflammatory syndromes generate

Table I. Paediatric patients with IRP reported in the English medical literature.

Study	Patients (n)	Age (years) at onset	Gender	Therapy
Yagizi (55), 1998	3	5	Male	Asprin, pericardiocentesis, prednisone, aspirin, colchicine
		4	Male	Diclofenac, colchicine
		14	Male	Pericardiocentesis, colchicine
Brucato (56), 2000	1	14.5	Male	NSAIDs, methylprednisolone, prednisone, iv immunoglobulins, aspirin, indomethacin, colchicine
Raatikka (13), 2003	15	mean 11.6	9 Males 6 Females	NSAIDs, prednisolone, methotrexate, azathioprine, cyclosporine, colchicine
Picco (25), 2009	3	14	Female	Prednisone, colchicine, anakinra
		12	Male	Prednisone, colchicine, anakinra
		13	Female	NSAIDs, prednisone, colchicine, methotrexate, anakinra
Scardapane (64), 2012	1	11	Male	NSAIDs, prednisone, colchicine, anakinra

a proinflammatory state with activation of the inflammasome, a complex of distinct group of proteins which convert inactive prointerleukin 1 beta to the active proinflammatory cytokine IL-1 beta (32).

IRP mimics autoinflammatory diseases as it is characterised by periodic recurrences, alternating with symptom-free intervals (33); a family history is present in about 10% of patients (34, 35).

In a recent work, Cantarini *et al*. have shown that TRAPS is a cause of recurrent pericarditis in 6% of unselected patients with IRP (36). The authors suggested that mutation analysis in TNFRSF1A and in MEFV should be considered in patients of Mediterranean origin with recurrent pericarditis, especially with multiple recurrences refractory to conventional therapies and colchicine.

Medical therapy

Treatment of IRP in children is not standardised and largely empiric due to the lack of randomised trials. The main objectives of therapy are to treat single acute episodes and to prevent or limit recurrences (37).

NSAIDs

NSAIDs are recommended as first-choice treatment for acute and recurrent pericarditis, with the goal of therapy being the relief of pain and the resolution of inflammation (3, 38). Still, unsatisfactory results are often reported when NSAIDs are used alone (12, 13). Some of these failures may be partially due to low dosages or to overly short courses of therapy (20).

Some authors recommend that a full anti-inflammatory dose should be prescribed and the attack dose should be maintained until complete normalisation of the CRP; afterwards, a gradual tapering of the drug should be considered (17, 20, 21).

The choice of the specific NSAID should be based on the efficacy and tolerability in the single patient and the presence of concomitant diseases and therapies (21).

These drugs are generally well tolerated in children. The most common side effects are gastrointestinal symptoms such as nausea and appetite loss. Other side effects include behaviour disturbance, headache and pseudoporphyria rash, which is more common in fair skinned children (39, 40). Aspirin (70–100 mg/kg b.w./day) should be used with caution due to the associated risk of Reye's syndrome (41, 42). Ibuprofen (30–40 mg/kg b.w./day) is generally well-tolerated; however, gastrointestinal bleeding, compromised renal function and an increased risk of cardiovascular events are reported in children receiving this drug (41).

Indomethacin can be also used in paediatric patients and it is equally well tolerated at doses of 1–2 mg/ kg b.w./ day; however, like other NSAIDs, it can cause gastrointestinal bleeding, platelet and renal dysfunction because of the ability to decrease cerebral, gastrointestinal and renal blood flow (42).

There are no specific recommendations regarding the use of NSAIDs in IRP both in children and in adults (21). In our experience, ibuprofen and naproxen are first-line drugs and the use of indomethacin is reserved to more aggressive disease.

Corticosteroids

The use of corticosteroids in acute and recurrent pericarditis remains controversial. In paediatric patients, these drugs are recommended only temporarily, if severe symptoms are present, and in patients unresponsive to NSAIDs (13). Long-term use of steroids should be limited also for the known effects of these drugs on bone mineral metabolism and growth and the induction of permanent striae rubrae (12, 37).

Corticosteroids effectively suppress pericardial pain and inflammation during acute attacks; however, their efficacy in preventing relapses has been questioned. Raatikka *et al*. (13) used corticosteroids in 11 paediatric patients during the initial attack of pericarditis and NSAIDs alone in 4 patients. Over a follow-up period of 4 years the authors observed that 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 treated only with NSAIDs. Remission at 4 years was achieved by 5 of 11 patients of the first group and 2 of 4 of the second group (13).

These data were confirmed in some prospective, randomised, open label and controlled studies in adult IRP patients by Imazio *et al*., who demonstrated that the previous use of corticosteroids in the treatment of acute pericarditis was an independent risk factor for recurrences, whereas the use of colchicine was found to be protective (4, 5).

In a multi-centre study, Artom *et al*. addressed the hypothesis that pretreatment with corticosteroids exacerbates and extends the course of recurrent pericarditis and also attenuates the efficacy of colchicine in preventing recurrences. In this study, 119 patients with IRP treated with colchicine were selected from published studies and case reports; of these 60% had been previously treated with corticosteroids. In patients previously treated with

corticosteroids, a significantly higher number of recurrences was documented (43 *vs*. 13% *p*=0.02); moreover, the average number of relapses per patient, after colchicine treatment, was significantly higher (0.65±0.99 *vs*. 0.18±0.56) among those with previous corticosteroid treatment (43). A possible explanation is that, as acute pericarditis is often of viral origin, corticosteroids can promote viral replication thus facilitating the recurrence of pericarditis (44, 45).
Moreover, in a retrospective study, Imazio *et al*. showed that patients treated with high doses of prednisone (1.0 mg/kg b.w./day) (group 2) had a higher rate of severe side effects compared to patients treated with lower doses (prednisone 0.2–0.5 mg/kg b.w./day) (group 1). Besides, a higher recurrence rate was recorded in group 2 than in group 1, as well as a higher frequency of disease-related hospitalisations (46). Consequently, the authors suggest that low doses of prednisone are more effective than high doses in reducing recurrences and hospitalisations, as well as inducing considerably fewer side effects (46).
In conclusion, corticosteroid use is rarely indicated for IRP, especially in children. When the use of steroids is really required, low doses are recommended to control attacks. If symptoms recur during steroids tapering, every effort should be made not to increase the dose or reinstitute corticosteroids and to control symptoms by commencing or increasing the doses of NSAID, eventually adding acetaminophen and/or analgesics to obtain better symptoms control (20, 37).
A very slow steroid tapering only after stable remission with symptoms resolution and normalisation of CRP is the key to successful management of the disease (37).

Colchicine

Colchicine has been used for the treatment and prevention of gouty attacks as well as for the treatment of FMF. The exact mechanism of colchicine action is not fully understood; it is thought to decrease leukocyte motility and phagocytosis, reducing the inflammatory response (47). In recent years, some authors have proposed new mechanisms of action of colchicine consisting in the inhibition of pore formation, induced by activation of P2X receptors (48).
In 1987 Rodriguez de la Serna *et al*. (49) used this drug for the first time with success in adult patients with IRP, on the basis of the proven efficacy of colchicine in preventing relapses of serositis in FMF (50). At doses of 1–2 mg per day, colchicine is safe even when given continuously for decades. Usual side effects are gastrointestinal (up to 10–15% of cases) including nausea, vomiting, diarrhea, and abdominal pain that may resolve with dose reduction or fragmentation (47). Many retrospective studies support the use of colchicine in recurrent cases of pericarditis (23, 51-53). The COlchicine for acute PEricarditis (COPE) trail provides evidence that colchicine in combination with aspirin or prednisone is safe and efficacious in the treatment of the first episode of acute pericarditis, as well as in the prevention of recurrences (4). Colchicine therapy led to a clinically and statistically significant benefit over conventional treatment also in the CORE trial (COlchicine for REcurrent Pericarditis) (54). In this prospective, randomised, open-label study, 84 patients who had reported one episode of recurrent pericarditis were randomly assigned either conventional treatment with aspirin alone (group 1) or conventional treatment plus colchicine (group 2). At 18 months, recurrence rates were 50.6% in group 1 *vs*. 24.0% in group 2 (*p*=0.02), with an absolute risk reduction of 26.6%. Recently, 120 patients with a first episode of recurrent pericarditis have been enrolled in the CORP trial (COlchicine for Recurrent Pericarditis), the first prospective, randomised, double-bind, placebo-controlled, multicentre trial. Patients were randomised to receive placebo or colchicine in addition with a conventional treatment. The recurrence rate was 24% in the colchicine group and 55% in the placebo group (absolute risk reduction 0.31 [95%CI 0.13–0.46]). These results provide a strong evidence for the use of colchicine and also show that colchicine might be considered a first-choice therapy for patients with IRP (5, 54). The limitation of the CORP trial is that the study recruited only adults and so, as reported by the authors, the results cannot be applied to children (5).
Yagizi *et al*. were the first authors that reported the use of colchicine in children affected by IRP. They analysed three paediatric patients, who, after a multi-drug therapy with NSAIDs and corticosteroids, responded remarkably well to colchicine at a dose of 0.5–1 mg daily (55). In another report, an adolescent boy was effectively treated with colchicine after multiple unsuccessful attempts to withdraw corticosteroids therapy (56). In the experience of Raatikka *et al*. (13), colchicine did not prevent pericarditis recurrences. They administered colchicine to 4 paediatric patients who had relapses despite corticosteroid treatment. Patients had 3 to 10 recurrences (mean 5.8) during a period of 6 to 27 months (mean 13.3 months) on colchicine (13). It should be underlined that the important paper by Raatikka *et al*. was retrospective and observational, and not designed to assess the problem of therapy, with the interactions between different drugs, dosages and combinations (57).
The recommended dose is 0.5 mg/day for children ≤5 years and 1.0–1.5 mg/day in two to three divided doses for older children (47).

Other immunosuppressive therapies

Immunosuppressive drugs should be considered in patients who do not respond to conventional therapy or who experience severe complications related to steroid treatment. The evidence for their use comes from observational findings and case reports (58). The choice should be based on the least toxic agent, and treatment should be tailored to each individual patient. Azathioprine has been used with variable success particularly in adults (26), while methotrexate did not prevent recurrences in 5 paediatric patients (13). More recently, a larger series of 46 patients treated with azathioprine has been reported, the age ranging from 11 to 71 years, average 39.7 years (26).

Biologic therapies

Intravenous immunoglobulins

Human intravenous immunoglobulins

(hIVIgs) have been used in only one study by Peterlana *et al*. They reported four adult patients with IRP treated with monthly high dose hIVIgs (0.4 g/kg b.w. daily for 5 consecutive days). Three of these patients experienced a complete remission of the disease, the fourth patient was only partially responsive to therapy (27).

Specific biological agents

Biologics are genetically engineered drugs targeting specific sites of the inflammatory cascade such as cytokines, cell surface molecules, and adhesion molecule. A limitation of biologic therapies is that the response to treatment is not predictable, and careful safety monitoring is necessary due to the risk of infections, anaphylactic reactions, possible neurologic side effects and low response to vaccinations (42).

Anakinra

Anakinra, a recombinant IL-1β receptor antagonist, is approved for the treatment of rheumatoid arthritis and frequently used in the CAPS. It has been shown to be effective in small cohorts of therapy resistant adult-onset Still's disease, and paediatric systemic onset JIA (59-62).

Picco *et al*. describe a dramatic therapeutic response to IL-1β receptor antagonist (anakinra) in 3 paediatric patients with steroid-dependent IRP (25). The introduction of this drug led to a resolution of all clinical symptoms and normalisation of acute-phase reactants. After complete remission, treatment with anakinra was stopped and in a few weeks there was an exacerbation of the disease. With the reinstitution of anakinra, all symptoms disappeared again. At a mean follow-up of 6 months from the initial administration of the drug, none of the patients experienced a new relapse. According to the authors, although the duration of the follow-up is limited, the use of anakinra is able to prevent disease relapses (25). Cantarini *et al*. reported a similar positive experience with anakinra in a patient with a TNFRSF1A gene mutation (14). Three additional adult cases were reported by Vassilopoulos *et al*. (63).

We also obtained a rapid response to anakinra in a 11-year-old patient with steroid dependent IRP unresponsive to conventional therapy (64). In our patient, anakinra allowed a rapid steroid tapering and discontinuation of steroid therapy after 3 months. No relapse was observed during the follow-up period of 12 months after the discontinuation of corticosteroids. In this period, anakinra was never discontinued and no side effect was detected.

The remarkable response to anakinra treatment in IRP patients supports the hypothesis that IL-1β may have a role in the pathogenesis of this disease and suggests that IRP might be considered an as yet unidentified autoinflammatory disease.

Anakinra, therefore, seems to be an effective alternative for those IRP patients that continue to have frequent relapses despite colchicine and anti-inflammatory therapy, or show important steroid side effects or corticodependence.

However, numerous questions concerning the use of anakinra are still open. It is not clear when to discontinue the treatment and if the long-term therapy with anakinra can produce relevant side effects. Further controlled studies on the wider population and with longer follow-up are needed to establish the possible role of IL-1 blocking in the treatment of IRP.

Etanercept

Cantarini *et al*. reported the use of the etanercept, a TNF-α inhibitor, as a first-line therapy with excellent results in patients with RP who carry a mutation in TNFRSF1A, the gene of TRAPS (14). Etanercept can reduce corticosteroid requirement and also prevent flare-ups (65); however, the long-term benefits of the TNF inhibitor have yet to be evaluated (14).

Practical tips regarding the multidrug therapy of IRP in children

NSAIDs represent the mainstay of the therapy; the highly recommended rheumatological dose should be used if tolerated (20), and given every 8 hours according to the half-lives of the used drugs, at least during the acute attack. The dosage should not be decreased until the symptoms disappear and the normalisation of the CRP occurs (17). Only at that point should a gradual tapering be attempted. Colchicine should always be considered, starting with low doses (*e.g*. 0.5 mg) and eventually fractionated to improve gastrointestinal tolerability, if tolerated, it should then be increased. It is tempting to use corticosteroids, as they are very effective in suppressing the pain and in relieving the pericardial effusion. However, steroid treatment clearly tends to increase the number of relapses (4, 5, 54) and induces corticodependence (20, 43). Furthermore, the well-known side effects of corticosteroids are especially undesirable in growing children and adolescents. When deemed really necessary, low doses are effective (46), eventually fractionated, and with far less side effects. They should be tapered very slowly, particularly at low dosages, with each tapering done only in the absence of symptoms and with normal CRP (17). In cases of recurrence, every effort should be made not to increase the dose, but to fraction the total dose in two half-doses so as not to reinstitute corticosteroids and to control symptoms by commencing or increasing the doses of NSAID. Eventually adding acetaminophen and/or analgesics to obtain better symptom control will reassure patients and their parents until the attack is over in 1–3 weeks (20, 37). Corticosteroids are tapered and stopped first (weeks-months), than NSAIDs (other weeks-months) and lastly colchicine might be gradually tapered; this tapering might last months or even years. Anakinra might be considered for children who do not tolerate other therapies or may be considered as an alternative to low-dose corticosteroids in rare patients who do not respond to high dose NSAID plus colchicine, particularly in the cortico-dependent patients who require unacceptably high chronic doses of steroids (66). Anakinra should then be tapered gradually, always in absence of symptoms and with normal CRP. In these children, colchicine therapy might be continued to lower the risk of recurrence during or after Anakinra discontinuation, and NSAIDs might be again useful in that phase.

Conclusions

IRP is a rare disease in children whose pathogenesis (autoimmune or autoinflammatory?) remains to a certain extent unexplained. NSAIDs represent the mainstay of the therapy and corticosteroids use should be restricted. Colchicine should always be considered, since it halves the recurrence rate. New biologic drugs such as IL-1 inhibitors are probably the therapeutic frontiers in the care of IRP.

Key messages

- Recurrent pericarditis in children is a common complication of pericarditis with a probable autoimmune pathogenesis.
- Current management is largely empiric because of the lack of randomised trials.
- Biologic drugs are promising agents in the treatment of the disease

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