Late cardiac assessment in children diagnosed with post-streptococcal reactive arthritis: a long-term study

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Abstract

Objective

Unlike rheumatic fever (RF), the association of post-streptococcal reactive arthritis (PSRA) and carditis is controversial. The American Heart Association recommends anti-streptococcal prophylaxis for PSRA for one year, repeating echocardiogram and discontinuation of prophylaxis if normal. In this study the possibility of late cardiac involvement was investigated in a cohort of children with PSRA.

Methods

Children diagnosed with PSRA and followed at the Paediatric Rheumatology Units at two medical centres in Israel had echocardiography carried out by a paediatric cardiologist, at least 1 year following diagnosis.

Results

146 patients with PSRA met the study criteria. Of these, 69 had undergone echocardiography 1–6.9 years (mean 3.6 years ± 1.5 years) after diagnosis. All had normal major parameters. Twenty (29.0%) patients had minimal cardiac findings, including 5 (7.2%) mild mitral insufficiency, 12 (17.4%) minimal mitral insufficiency, 2 (2.9%) mild tricuspid insufficiency and one patient (1.4%) had very mild, aortic insufficiency. Of the 77 patients who did not have echocardiography, 31 were randomly excluded from the initial study list, 26 refused to undergo echocardiography, and 20 were lost to follow-up. All were asymptomatic according to their medical record or telephone questionnaire. There were no significant differences in clinical or demographic data between those with or without echocardiography

Conclusions

No late cardiac involvement was found in our paediatric PSRA patients. Therefore, different approaches to antibiotic prophylaxis for PSRA and ARF are probably suggested. A prospective, controlled study is needed to definitively assess the necessity of prophylaxis in PSRA.

Key words

post-streptococcal reactive arthritis, heart involvement, rheumatic fever, children, anti-streptolysin O

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Introduction

Current knowledge supports the concept that post-streptococcal reactive arthritis (PSRA) is distinct from acute rheumatic fever (ARF) based on several aspects of the two entities. Demographically, the age distribution of PSRA appears to be bimodal, with a peak at 8–14 years of age and another at 21–37 years. In contrast, ARF has a single peak incidence in childhood at around age 12 (1). In ARF, arthritis usually occurs 2 to 4 weeks after group A streptococcus (GAS) pharyngitis, while in PSRA arthritis appears approximately 7–10 days after the infection. PSRA arthritis is additive and persistent and can involve large and small joints or the axial skeleton. In ARF, the arthritis is migratory and transient, and usually involves the large joints (1-5). Furthermore, the arthritis of ARF responds dramatically to acetylsalicylic acid or non-steroidal anti-inflammatory drugs (NSAIDs) such as naproxen, while the response to this therapy in PSRA is much more modest (6).

Reports regarding heart involvement in PSRA, as opposed to ARF, are also conflicting (7-10), The 2009 American Heart Association (AHA) scientific statement recommends that patients with PSRA should be observed carefully for several months, for clinical evidence of carditis (6). They suggest secondary prophylaxis for up to one year after the onset of symptoms and discontinued if there is no evidence of carditis at one year. If valvular disease is detected, the patient should be classified as having had ARF and secondary prophylaxis continued. However, the effectiveness of this strategy is not well established. The level of evidence (LOE) for this recommendation is C - "only consensus opinion of experts, case studies, or standard of care", and IIb - usefulness/efficacy, less well established by evidence/opinion.

In light of the numerous differences between PSRA and ARF, we consider that PSRA is a distinct entity that does not include cardiac effects. The aim of this study was to evaluate the presence of late cardiac involvement in children with PSRA, a few years after the diagnosis and termination of antibiotic therapy.

Patients and methods

Children with defined PSRA, younger than 18 years at presentation, who were followed at the Paediatric Rheumatology Units at Meir and Kaplan Medical Centres, were included in the study. Clinical, demographic and laboratory data were gathered by charts review, and echocardiography, performed by paediatric cardiologists, was carried out at least 1 year after diagnosis.

We based our definition of PSRA on that of Ayoub and Ahmed who proposed the following diagnostic criteria: "Arthritis of acute onset, symmetric or asymmetric, usually non-migratory, which can affect any joint and is persistent or recurrent. At best, the arthritis is poorly responsive to salicylates or NSAIDs. The arthritis is accompanied by evidence of antecedent GAS infection, but there are no other symptoms or signs to fulfill the modified Jones criteria for the diagnosis of ARF (11)." Our inclusion criteria were patients younger than 18 years at the time of diagnosis of PSRA, with onset at least a year before the start of the study.

Evidence of antecedent GAS infection was determined by one of the following methods: A positive throat culture at the time of diagnosis, and/or anti streptolysin titer of more than 400 IU/ml (>2 times higher than the normal value in our juvenile population) at the time of diagnosis

Statistical analysis

Data are presented as mean ± standard deviation. Unpaired *t*-test was used to describe the results. Analyses were performed using SPSS v. 21 (SPSS, Inc. Chicago, Illinois). Statistical significance was set at $p<0.05$. Data collection was approved by the hospitals Ethics Committees in compliance with the Declaration of Helsinki. Informed consent was obtained in all cases prior to the echocardiography

Results

One hundred and forty-six PSRA patients fulfilled the study criteria. Of these, 69 had undergone echocardiography from 1 to 6.9 years (mean 3.6 years ± 1.5 years) after diagnosis and were included in the study. Of the 77

patients who did not complete echocardiography, 31 were randomly excluded from the initial study list, 26 refused to undergo echocardiography, but were asymptomatic according to their medical record or telephone questionnaire, and 20 were lost to follow-up (Fig. 1).

Of the 69 patients who underwent echocardiography, 38 (55.1%) were male and 31 (44.9%) were female. Ages at the time of diagnosis ranged from 2 to 16.5 years, (average age 8.32 years ±3.2 years).

Of the 69 study patients, 31 (44.9%) had a positive throat culture. Among this group, 14 (20.3%) had also an anti-streptolysin O (ASLO) titer of more than 400 IU/ml. The diagnosis was made based on elevated ASLO titers alone in the remaining 38 (55.1%) patients. There was no differences between the group that was diagnosed by positive throat culture, to the group that was diagnosed by high ASLO titer, except for the polyarthritis pattern which was more common in the group with the high ASLO (Table I).

Multiple large joint involvement occurred in 18 (26.1%) patients, 10 (14.5%) had small and large joint involvement and 39 (56.5%) had monoarthritis of a single large joint. Only 2 (2.9%) patients had axial involvement.

A total of 31 patients (44.9%) did not receive prophylactic antibiotic treatment. The rest received prophylactic antibiotic treatment for 1 to 48 months (average 15.32±13.88 months). Twenty three patients of the 38 patients that had prophylactic antibiotic treatment were treated for one or more years, 15 patients were treated prophylacticly for less than one year (Fig. 1). The antibiotic administered to the patients was penicillin either given daily per os or once a month by injection.

There were no statistically significant demographic, clinical or laboratory differences between those had undergone an echocardiography examination (n=69) and those who had not (n=77), expect for the number of patients treated with prophylactic antibiotics (Table II).

All 69 study patients had an echocardiography at least one year after diagnosis. None had any cardiac symptoms or clinical signs. Twenty patients had minimal findings: 5 (7.2%) had mild mitral insufficiency; 12 (17.4%) had minimal mitral insufficiency; 2 (2.9%) had mild tricuspid insufficiency and one patient (1.4%) had very mild aortic insufficiency (Fig. 1; Table III). All findings did not meet the 2012 WHF criteria for echocardiographic diagnosis of rheumatic heart disease, and did not meet the Doppler echocardiographic criteria for Pathological mitral or aortic regurgitation (12). Anatomically all valves were intact: the mitral valve with no chordal thickening or restricted leaflet motion, the aortic valve with no irregular or focal thickening, coaptation defect or restricted leaflet motion. All findings were considered non-significant by the paediatric cardiologists.

Of the 69 study patients, 21 (30.4%) had recurrent episodes of PSRA. Of the 21 patients with recurrent episodes, 2 had

Fig. 1.

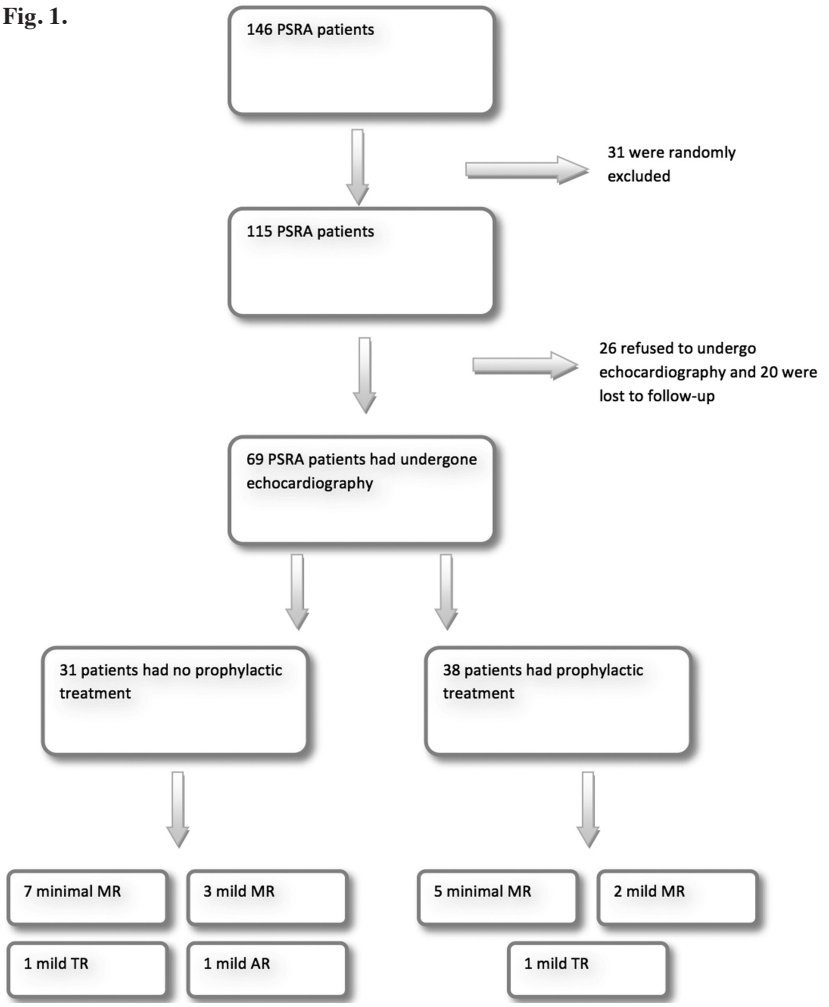

Table I. Demographic, clinical and laboratory comparisons between the PSRA group with a positive throat culture and the PSRA group with elevated ASLO titers.

	positive throat culture (n=31)	elevated ASLO titers (n=38)	*p*-value
Female (%)	12 (38.7%)	19 (50%)	0.348
Average age (years)	8.25 ± 2.9	8.39 ± 3.4	0.863
Number treated prophylacticly (%)	13 (41.9%)	18 (47.4%)	**0.652**
Average duration of prophylactic treatment (month)	15.4 ± 14.8	14.7 ± 13	**0.810**
Patients with polyoarthritis (%)	8 (25.8%)	22 (77.9%)	***0.007***
Patients with minimal MR (%)	7 (22.6%)	5 (13.1%)	**0.304**
Patients with mild MR (%)	3 (9.7%)	2 (5.3%)	**0.651**
Patients with mild TR	0	2 (5.3%)	**0.498**
Patients with very mild AR	0	1 (2.6%)	**1.000**

Table II. Demographic, clinical and laboratory comparisons between the group that underwent echocardiography and the group that did not.

	Echo group (n=69)	non-Echo group (n=77)	*p*-value
Female (%)	31 (44.9%)	27 (35.1%)	
Average age (years)	8.32	9	
Average ASLO titer (IU/ml)	880.8	853.2	
Number treated prophylacticly (%)	38 (55.1%)	28 (36%)	
Average duration of prophylactic treatment (months)	15.3	16.5	
Patients with monoarthritis (%)	39 (56.5%)	50 (64.9%)	

Table III. Echocardiography findings among the healthy population compared to ARF and PSRA patients.

	Healthy population [13-15]	ARF patients [19*]	PSRA patients**
Mild mitral insufficiency	2.4-12.1%	56.98%	7.2%
Mild tricuspid insufficiency	6.3-56.4%	19.35%	2.9%
Mild aortic insufficiency	1.1-2.1%	22.6%	1.4%

*all degrees of mitral, tricuspid and aortic insufficiency; **PSRA patients in our study.

mild MR found on follow-up echocardiography.

Discussion

Sixty-nine paediatric patients with PSRA were described, including their demographic and clinical data and late echocardiographic findings. No clinically significant late cardiac involvement was found in any patient. A minority had clinically insignificance findings on echocardiogram that did not require further follow-up.

From a review of the literature regarding heart involvement; there are conflicting reports: De Cunto *et al*. described 12 paediatric patients diagnosed with PSRA (7). One patient in this group developed classic ARF with valvulitis 18 months after the initial episode. She presented with arthritis of the elbow, left ankle and knee, and treated with one dose of benzathine penicillin G, at that time she did not fulfill the Jones criteria. Her cardiac examination was normal. After 18 asymptomatic months she developed acute migratory arthritis, chest pain, subcutaneous nodules and a grade 3/6 new murmur. She might have developed ARF, perhaps with no connection to the prior PSRA episode. Similarly, Ahmed *et al*. described 25 paediatric PSRA patients. Carditis was diagnosed in one patient 9 months after the onset of arthritis (10). In a retrospective study, Moorthy *et al*. described 40 paediatric patients with PSRA (8), among which 2 patients with a normal baseline echocardiogram developed findings after 12 months of follow-up (left ventricular systolic dysfunction, mitral, tricuspid and pulmonary insufficiency). In contrast, van Bemmel *et al*. recently described 60 adult patients diagnosed with PSRA who were not treated with antibiotic prophylaxis (4). After a median follow up of 8.9 years, there was no increased risk of valvular heart disease compared to the control group. Similarly, Simonini described 52 children with PSRA; all were treated with antibiotic prophylaxis for one year (2). After a median follow-up of 8 years, none of the patients had developed any clinical or echocardiographic evidence of valvular disease or cardiac involvement. Barash *et al*. described 152 paediatric PSRA patients, none of whom had late cardiac involvement (3).

In healthy children, the prevalence of tricuspid and mitral insufficiency detected by echocardiography, ranges from 6.3–56.4% to 2.4–12.1%, respectively (13-15). One patient in our study group had very mild aortic insufficiency, a finding that is also described in 1.1–2.1% of healthy children (13-15). It should be noted that ARF carditis is present in 35-55% of paediatric patients (16-18) and valvular insufficiency without carditis is present in most patients (19-21). As shown in Table II in our PSRA cohort, there was no carditis; valvular insufficiency did not meet the 2012 WHF criteria for echocardiographic diagnosis of rheumatic heart disease, and did not meet the Doppler echocardiographic criteria for pathological mitral or aortic regurgitation (12). Our findings were consistent with the findings in the general, healthy population and not similar to the incidence of valvular involvement in ARF.

The AHA recommends that PSRA patients should be treated with prophylactic antibiotics for one year following diagnosis (6). In our group of patients, the average duration of antibiotic therapy was 15.32 months, as suggested by AHA guidelines. Due to noncompliance, 31 children did not receive any antibiotic treatment. In this group, 23 children had a normal echocardiography at the end of the follow-up. Physiologic mitral insufficiency was found in 5 children, 2 had mild mitral insufficiency and one had very mild aortic insufficiency. These findings suggest that antibiotic prophylaxis might not be necessary for children with PSRA. In the past, case reports and small series of carditis in PSRA patients have been published (7-10). In contrast, in recent years the literature indicates that PSRA is a different entity than ARF with specific clinical, laboratory, genetic and demographic parameters and no cardiac involvement (2-4). It is possible that the previous reports of carditis in PSRA were based on a wrong diagnosis and that, in fact, these patients had ARF.

There are some limitations in this study. As in previous trials, a definite diagnosis of PSRA was challenging. The diagnosis of a GAS infection based on a single ASLO titer is problematic, since a change in titer is usually required for the diagnosis of acute streptococcal infection. However, due to the nature of our retrospective study, half of the cases were diagnosed according to a single measurement of ASLO antibodies. The repeated measurement method was not applicable in all cases. Also, the test for levels of anti-DNAse B, which is considered more sensitive for GAS infection, is currently unavailable in our participating medical centers. In light of these limitations, we decided on an ASLO antibody titer threshold of 400 IU/ml, which is twice the normal value for this age group in our area, to indi-

cate a recent GAS infection. Similar upper limit of normal values were reported in a USA study (22). This high threshold was chosen so that the diagnosis of PSRA in our study would be accurate despite the single ASLO measurement. Using this high ASLO threshold caused the study group to be smaller than first anticipated. There were children who were diagnosed with PSRA in the clinic by experienced paediatric rheumatologists and treated accordingly, but not included in the study because of borderline ASLO titers and lack of repeated measurements. It is to be noted that no cardiac involvement was found in this group either.

When analysing the two group separately there were no statistically significant differences between the groups, except for the polyarthritis pattern which was more common in the group with the ASLO which might add to this diagnosis.

Another limitation of the study is that 77 patients of the initial study group did not complete echocardiography. Table II demonstrates that there were no statistically significant demographic, clinical or laboratory differences between those had undergone an echocardiography examination and those who had not, expect for the number of patients treated with prophylactic antibiotics. This difference could be explained by the fact that the group that had not undergone an echocardiography examination was probably less compliant in both taking the prophylactic treatment and completing the echocardiography. The fact that the two groups demographics and clinical characteristics were similar suggests that the patients studied were likely to represent a larger population

In summary, in this study we did not find late cardiac involvement in paediatric PSRA patients. Better diagnostic criteria for PSRA are needed, like the regression mathematical formula based on four significant diagnostic discriminators suggested by Barash *et al*. The discriminators were a lower sedimentation rate and CRP at disease onset, longer time for resolution of joint symptoms after starting anti-inflammatory therapy, and higher recurrence rate of arthritis after discontinuing anti-inflammatory therapy, (3). Using these discriminators together with the criteria for previous GAS infection will prevent over- or under diagnosis of this disease. Emphasis should be made to the treating physician to do every effort to collect 2 ASLO samples 2–4 weeks apart in order to detect a 2-fold increase in the ASLO titer. Our study shows that prophylactic antibiotic treatment may not be needed for PSRA. Additional, large, prospective studies are needed, which will follow PSRA patients without prophylactic antibiotic treatment and include a control group of healthy children, so that proper treatment and follow-up for PSRA patients can be established. This might be done by an international multicenter study, led by large research group like PRINTO, with cooperation of cardiology units for the detection of late cardiac involvement.

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