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Original article

A retrospective study: Acute rheumatic fever and post-streptococcal reactive arthritis in Japan

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ARF, Acute rheumatic fever; PSRA, post-streptococcal reactive arthritis; GAS, group A streptococcal; NSAIDs, non-steroidal anti-inflammatory drugs; RHD, Rheumatic heart disease; CRP, C-reactive protein; ASO, antistreptolysin O

ABSTRACT

Background: Acute rheumatic fever (ARF) and post-streptococcal reactive arthritis (PSRA) are immune-mediated consequences of group A streptococcal pharyngitis. ARF has declined in developed nations. No prevalence survey of PSRA has been conducted. This study evaluated the incidence and characteristics of ARF and PSRA in Japanese children.
Methods: From 2010 to 2015, ARF and PSRA were evaluated using clinical data retrospectively collected by chart review from 528 hospitals.
Results: From 323 hospitals (61% response rate), 44 cases of ARF and 21 cases of PSRA were reported. Patients with ARF and/or PSRA were mainly from large cities in Japan. The mean age of ARF occurrence was 8.5 years, and the ratio of female/male patients was 16:28. Major manifestations in the acute phase included carditis, 27 cases (61.4%); polyarthritis, 22 cases (50%); erythema marginatum, 7 cases (15.9%); Sydenham chorea, 3 cases (6.8%); and subcutaneous nodules, 1 case (2.3%). Twenty-one (58.3%) patients had migratory arthritis. During the follow-up period, 6 patients (13.6%) showed mild carditis. For PRSA, the mean age was 8.2 years, and the ratio of female/male patients was 12:9. Six (28.6%) patients had monoarthritis, and 4 (19%) patients had migratory arthritis. No patient had carditis.
Conclusions: Although ARF and PSRA are rare in the Japanese pediatric population, substantial numbers of patients with both conditions were identified in this study. We observed a high incidence of arthritis and carditis in ARF patients. No PSRA case was complicated with carditis. General pediatricians need to have updated information about ARF and PSRA, even in industrialized countries.

Introduction

Acute rheumatic fever (ARF) and post-streptococcal reactive arthritis (PSRA) are non-suppurative complications of group A streptococcal (GAS) pharyngitis.[1] ARF affects the joints, heart, brain, skin, and subcutaneous tissue. Cardiac involvement is the most serious manifestation of ARF. ARF has shown a marked decrease in incidence in developed countries, including Japan, with increasing standards of hygiene and access to health care being the major determinants of this change. In a recent systematic review of prospective population-based studies, the reported incidence of ARF ranged from 5 to 51 per 100,000 persons worldwide in the 5 to 15-year-old age group.[2] The highest incidence (100–200 per 100,000 persons) was documented in Eastern Europe, the Middle East, Asia, and Australia.[3] In contrast, the lowest incidence of 0.5–3 per 100,000 persons per year was found in America and Western Europe.[4] However, focal outbreaks of ARF have been reported in industrialized countries, often in the poor and in minority groups.[5]

PSRA is defined as arthritis in one or more joints in a patient who does not fulfill the Jones criteria for a diagnosis of ARF. Some authors consider PSRA as part of the spectrum of ARF, while other authors consider it as a different entity.[6–8] PSRA in children has only been reported in case reports and retrospective studies, and there are only a few studies about ARF and PSRA in Japanese children in the twenty-first century.[9]

The aim of this study was to investigate the incidence of ARF and PSRA in Japanese children and to ascertain the characteristics of ARF and PSRA.

Methods

This was a retrospective study of medical records. We sent a questionnaire to the 528 hospitals that qualified as the pediatric specialist training facilities belonging to the Japan Pediatric Society.

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We evaluated pediatric patients who were diagnosed as ARF and PSRA, and treated by attending pediatrician. We searched for patients diagnosed between the years 2010 and 2015 with ARF according to the revised Jones criteria of 1992; PSRA was diagnosed as arthritis involving one or more joints and associated with proven group A streptococcal infection in a patient not fulfilling the Jones criteria. The medical charts of these patients were reviewed, and all clinical and laboratory data were summarized.

Statistical analysis

Nonparametric comparisons of group means were conducted using the Mann–Whitney *U* test. Proportions were compared using the Fisher exact test. A P-value of less than 0.05 was considered significant for all tests.

This retrospective study was approved by ethical committee of Saitama Children's Medical Center (2015-02-012).

Results

Of the 528 hospitals who received the questionnaire, 323 hospitals (61%) responded. A total of 65 patients were reported, including 44 cases of ARF and 21 cases of PSRA. The annual number of ARF and PSRA patients from 2010 to 2015 is shown in Table 1. The medium age of onset was 8.5 (3–15) years for ARF and 8.2 (2–15) years for PSRA. A total of 63.6% of patients with ARF and 42.9% of patients with PSRA were boys. There was no significant difference between the two groups regarding age and sex. There was a slight predominance of male patients in ARF cases, whereas there was a slight predominance of female patients in PSRA cases. Approximately half of patients in both groups had histories of GAS pharyngitis. The latent period from pharyngitis was predominantly shorter in patients with PSRA. Patients with ARF had carditis (61.4%), arthritis (82%), chorea (6.8%), erythema marginatum (15.9%), and subcutaneous nodules (2.3%). Patients with PSRA had arthritis (100%) and subcutaneous nodules (4.8%), but no carditis, chorea, or erythema marginatum. Twenty-seven patients with ARF had carditis at the acute phase of the disease, mitral regurgitation 21/27 (77.8%), aortic regurgitation 14/27 (51.9%), and pericardial effusion 7/27 (25.9%) (Table 2).

High fever was recorded in 38 patients with ARF (86.4%) and 14 patients with PSRA (66.7%). Nine patients with ARF had prolonged PR intervals with electrocardiography, but no patient with PSRA had prolonged PR intervals (P = 0.02). The levels of C-reactive protein (CRP) and antistreptolysin O (ASO) were significantly higher in the ARF group than in the PSRA group (P < 0.01). ESR was not different between the patient groups.

In Table 3, 58.1% of patients with ARF had significantly more migratory arthritis compared to 19% of the patients with PSRA (P < 0.01). Comparing ARF and PSRA, arthritis affected the knee joint in 66.7% vs. 61.9%; ankle, 33.3% vs. 14.3%; wrist, 22.2% vs. 33.3%; elbow, 19.4% vs. 4.8%; finger, 5.6% vs. 28.6%; and hip, 33.3% vs. 38.1% of cases, respectively. There were no differences between the two groups regarding arthritis that occurred in the knees, ankles, hands, elbows, and hips except in the small joints of the fingers. Arthritis of the fingers in patients with ARF was significantly less than in patients with PSRA (P = 0.02). Monoarthritis did not differ between the two groups (ARF, 11.1% and PSRA, 28.6%).

Table 1
Number of children with ARF and PSRA each year.

Year	2010	2011	2012	2013	2014	2015	Total
ARF	5	6	6	6	8	13	44
PSRA	1	4	2	3	6	5	21

ARF, acute rheumatic fever; PSRA, post-streptococcal reactive arthritis.

Table 2
Characteristics of patients affected by ARF and PSRA.

	ARF (N = 44)	PSRA (N = 21)	P
Male/Female	28/16	9/12	0.09
Age at diagnosis (years)	8.5 (3–15 years)	8.2 (2–15 years)	0.68
History of GAS infection	20 (45.5%)	10 (47.6%)	0.28
Latency period (weeks)	2.2 (1–8 weeks)	1.7 (1–4 weeks)	0.14
Polyarthritis	22 (50%)	6 (28.6%)	0.09
Carditis	27 (61.4%)	0 (0%)	<0.01
Mitral regurgitation, *n*	21	–	–
Aortic regurgitation, *n*	14	–	–
Pericardial effusion, *n*	7	–	–
Other cardiac complication, *n*	9	–	–
Chorea	3 (6.8%)	0 (0%)	–
Erythema marginatum	7 (15.9%)	0 (0%)	–
Subcutaneous Nodules	1 (2.3%)	1 (4.8%)	–
Fever	38 (86.4%)	14 (66.7%)	0.06
Elevated CRP and/or ESR	43 (97.7%)	19 (90.5%)	0.19
Increased CRP	10.7 ± 6.4 (n = 42)	3.5 ± 2.8 (n = 20)	<0.01
Increased ESR	69 ± 31.1 (n = 32)	56 ± 41.2 (n = 16)	0.06
Prolonged PR interval	9 (21.4%) (n = 42)	0 (0%) (n = 18)	0.02
ASO	1366 ± 1222 (n = 43)	1154 ± 2100 (n = 20)	<0.05

ASO, antistreptolysin O; ARF, acute rheumatic fever; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GAS, group A streptococcal; PSRA, post-streptococcal reactive arthritis. Results were shown as a mean ± standard deviation.

Table 3
Clinical characteristics of arthritis in patients with ARF and PSRA.

	ARF with arthritis (N = 36)	PSRA (N = 21)	P
Migratory arthritis, *n* (%)	21 (58.3%)	4 (19%)	<0.01
Knee arthritis, *n*	24 (66.7%)	13 (61.9%)	0.72
Ankle arthritis, *n*	12 (33.3%)	3 (14.3%)	0.12
Wrist arthritis, *n*	8 (22.2%)	7 (33.3%)	0.36
Elbow arthritis, *n*	7 (19.4%)	1 (4.8%)	0.12
Hip arthritis, *n*	12 (33.3%)	8 (38.1%)	0.72
Finger arthritis, *n*	2 (5.6%)	6 (28.6%)	0.02
Monoarthritis, *n*	4 (11.1%)	6 (28.6)	0.09

ARF, acute rheumatic fever; PSRA, post-streptococcal reactive arthritis.

Table 4
Treatment and outcomes of ARF and PSRA.

	ARF (N = 44)	PSRA (N = 21)
Acute phase treatment		
Antibiotic	42 (95.5%)	17 (81%)
NSAIDs	29 (65.9%)	16 (76.2%)
Corticosteroids	24 (54.5%)	1 (4.8%)
	ARF (N = 43)	**PSRA (N = 21)**
Secondary prophylaxis		
Antibiotic	43 (100%)	11 (52.4%)
Outcome		
Arthritis (more than 2 months)	0 (0%)	6 (28.6%)
RHD	6 (13.6%)	0 (0%)
Dead	1 (2.3%)	0 (0%)

ARF, acute rheumatic fever; NSAIDs, non-steroidal anti-inflammatory drugs; PSRA, post-streptococcal reactive arthritis; RHD, rheumatic heart disease.

Treatment and outcomes (Table 4)

Acute phase treatment

An initial course of antibiotic therapy was frequently used in both patients with ARF (95.5%) and patients with PSRA (81%). The use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with ARF and PSRA was 65.9% and 76.2%, respectively. NSAIDs used included aspirin in 19/44 (43.2%) patients, ibuprofen 5/44 (11.4%),