The resurgence of rheumatic fever in a developed country area: the role of echocardiography

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Abstract

Objectives. The annual incidence of ARF ranges from 5 to 51/100,000 population worldwide in the 5- to 15-year age group. In the past, there was a decline in the incidence of ARF; however, focal outbreaks have been reported. This study evaluated the incidence of ARF in 2007–08 in a region of a developed country compared with the previous decade.

Methods. A retrospective review of all admission records for ARF in Trieste between January 2007 and December 2008 was undertaken. The diagnosis of ARF was established by the Jones criteria according to the 1992 revision.

Results. Between January 2007 and December 2008: 13 cases of ARF were recorded, 11 females and 2 males. The estimated incidence was 23 and 27/100,000 population new cases each year, respectively, in the 5- to 15-year age group. Migratory polyarthritis occurred in 6/13, chorea in 7/13 and clinical carditis in 5/13 cases. Five out of 13 patients had only echocardiographic abnormalities, with no clinical cardiac manifestations. Another two patients did not fulfill diagnostic criteria for ARF, presenting with only three minor criteria, but they revealed silent carditis at echocardiography evaluation. During the follow-up, in one case the carditis receded and in the other it significantly improved.

Conclusions. Our experience underlines that ARF has not yet disappeared in industrialized countries. We observed a high incidence of chorea, always associated with mild carditis. Echocardiographic assessment should be routinely performed in all patients with suspected ARF in order to identify those subclinical cases of valvulitis that would otherwise pass undiagnosed without receiving proper prophylaxis.

Key words: Rheumatic fever, Echocardiography, Silent carditis, Chorea.

Introduction

ARF is a non-suppurative complication of Group A beta haemolytic streptococcal sore throat. It affects joints, heart, brain, skin and subcutaneous tissue. Cardiac involvement is the most serious manifestation of ARF, accountable for the major clinical and public health effects resulting from the long-term damage to heart valves. In a recent systematic review of prospective population-based studies, the reported incidence of ARF ranged from 5 to 51/100,000 population worldwide in the 5- to 15-year age group.

[1]. The lowest incidence rate of 0.5–3/100,000 per year was found in America and Western Europe [2]. In contrast, the highest incidence (100–200/100,000) was documented in Eastern Europe, Middle East, Asia and Australia [3].

The decline in the incidence of ARF in industrialized countries over the past four decades has been attributed to more hygienic and less crowded living conditions, improvement of access to medical care and introduction of antibiotics. Developing countries and some poor, mainly indigenous populations of wealthy countries, continue to experience a high burden of ARF.

However, focal outbreaks of ARF have been reported in industrialized countries, often in combination with the reappearance of certain rheumatogenic serotypes, as in the intermountain region of the USA since the mid-1980s [4].

In the past 10 years, the incidence of ARF in our region (Friuli Venezia Giulia, Italy) varied between 2 and
TABLE 1 Echocardiographic features of pathological left heart regurgitation

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
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<tbody>
<tr>
<td>Colour regurgitation jet in two planes</td>
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<tr>
<td>Regurgitation jet extending at least 2 cm</td>
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<tr>
<td>beyond the valve leaflets</td>
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<td>High-velocity signal at pulsed Doppler</td>
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<td>Holosystolic signal for mitral regurgitation</td>
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<tr>
<td>Holodiastolic signal for aortic regurgitation</td>
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4/100 000 new cases per year (L. Lepore and L. Ronfani; 2009, data not published) in the 5- to 15-year age group. The present report describes the focal outbreak of ARF observed in Trieste, the capital of Friuli Venezia Giulia, between January 2007 and December 2008.

Methods

A retrospective review of all admission records for ARF in our area between January 2007 and December 2008 was undertaken. The clinicians from all other paediatric units of Friuli Venezia Giulia were asked to calculate the incidence of ARF in the same period on the basis of diagnosis of the admitted patients (all patients with ARF were hospitalized in our region). The diagnosis of ARF was established by the Jones criteria according to the 1992 revision by the American Heart Association [5].

Independent of clinical heart murmur detection, all patients suspected to have ARF underwent cardiological assessment [ECG and two-dimensional (2D) colour-flow Doppler echocardiography] by a well-trained paediatric cardiologist with experience in ultrasound assessment. Echocardiographic exams were performed using a GE Vivid 3 ultrasound system, with a 6.7 or a 3 MHz probe, according to the patient’s size. Echocardiographic modifications indicative of subclinical valvulitis [6] were based on Doppler characteristics of the valvular regurgitation (Table 1).

We considered only mitral or aortic regurgitation; mild pulmonary or tricuspid regurgitation have been excluded because they are frequent in normal subjects [7]. Valvular regurgitations have been graduated according to the criteria of the American Heart Society of Echocardiography [8].

Clinical, laboratory, echocardiographic and demographic data from patients with a diagnosis of ARF were collected. Demographic data included date of birth, age of onset of ARF, address with zip code and family history. All patients were asked whether they had experienced an antecedent sore throat and whether they received antibiotic therapy. In all patients, an antecedent group A streptococcal antibody titre was measured and a significantly elevated or increasing serum streptococcal antibody titre was considered to be evidence of an antecedent group A Streptococcus (GAS) infection.

Results

Between January 2007 and December 2008, 13 cases of ARF were recorded, 11 females and 2 males. All cases were resident in Trieste. The incidence was 23/100 000 new cases for the year in 2007 and 27/100 000 in 2008 in the 5- to 15-year age group. Another two patients presented three minor criteria and silent carditis, not fulfilling diagnostic criteria for ARF.

In the rest of the region, the incidence of ARF varied from 2 to 4/100 000 per year, respectively, in the 5- to 15-year age group, the same as observed in the past decade in the city of Trieste.

The median age of patients was 8 (range 5–13) years. Out of 13 patients, 10 had an antecedent history of pharyngitis, and 2 out of 13 received antibiotic therapy (oral amoxicillin). Throat culture or rapid antigen test at the time of diagnosis of ARF was performed in 6 out of 13 patients and was positive in 3. Throat culture was negative in all cases in which an antecedent antibiotic treatment was given. In all cases, evidence of a recent GAS infection documented by significantly elevated or increasing serum anti-streptococcal antibody titres was found. Migratory polyarthritis occurred in six patients.

Chorea occurred in 7 out of 13 patients, all females. All patients with chorea presented associated carditis: four patients with clinical carditis and three with only echocardiographic abnormalities (silent carditis). In five patients, chorea was the clinical presentation of rheumatic disease. None presented erythema marginatum or subcutaneous nodules. Arthralgias were present in 7 out of 13 patients.

Nine patients presented fever. Acute-phase reactants (APRs) (ESR > 30 mm/h and/or CRP > 0.5 mg/dl) were elevated in 12 out of 13 patients. None presented prolonged PR interval on the electrocardiogram. (Patient characteristics are shown in Table 2).

All children received 10 days of orally administered amoxicillin followed by secondary antibiotic prophylaxis. Patients with migratory arthritis and those with carditis were treated with oral salicylates 75 mg/kg/day in three to four divided doses for 3–5 days, followed by 50 mg/kg/day until normalization of the APRs. Three patients received CSs (prednisone 2 mg/kg/day) for carditis.

Five patients with chorea (ambulation, self-feeding and speech impairment) received CSs (2 mg/kg/day) with complete resolution of symptoms in four within 2 months. In one patient, steroid therapy induced only a mild improvement of chorea symptoms; while valproate and intravenous immunoglobulins (IVIG) (2 g/kg) brought complete resolution of symptoms within 9 months. All patients received secondary antibiotic prophylaxis. The regimen of choice was a single i.m. injection of benzathine penicillin 1.2 million IU every 4 weeks or penicillin V 250 mg, twice a day. The duration was established according to the current guidelines [9].

Clinical carditis occurred in 5 out of 13 patients: 4 had isolated mitral insufficiency and 6 combined mitral and aortic insufficiency. All patients with clinical carditis had pathological valvular regurgitation at echocardiography. Five out of 13 had only echocardiographic abnormalities...
without auscultatory evidence (Table 3). In all patients carditis recovered without sequelae.

Another two patients (Table 3: Patients 6 and 7) presented with only three minor criteria, severe painful arthralgias with limitation of joint movement, fever and elevated APR with significantly elevated ASO, so they did not fulfil diagnostic criteria for ARF. However, both of them revealed silent carditis at echocardiographic evaluation: the first mitral regurgitation and the second mitral and aortic regurgitation. During the follow-up, in the first case the mitral insufficiency had ceased and in the other the mitral regurgitation jet had significantly reduced after treatment from 2.2 to 0.8 cm in length, while the aortic insufficiency disappeared, confirming an acquired disease. In these two cases, the diagnosis of ARF was not formalized; however, they were prudentially treated with secondary prophylaxis.

### Discussion

Focal outbreaks of ARF have been reported in industrialized countries, often in combination with reappearance of certain rheumatogenic serotypes. We report the first resurgence of ARF that occurred in our city in the past 10 years. In our series, all patients came from middle–upper classes, as observed in the past [10].

Eight out of 13 patients presented an antecedent history of clinical signs or symptoms suggestive of streptococcal pharyngitis according to McIsaac score [11]; only three patients received a bacteriological confirmation and two received a correct antibiotic treatment.

The lack of an appropriate antibiotic therapy could have contributed to the observed resurgence. A possible explanation might be that historical decline in the incidence of ARF has reduced the attention to treatment of streptococcal pharyngitis in order to prevent this complication. On the other hand, the focality of this recrudescence might be explained by the resurgence of rheumatogenic strains, which, unfortunately, we were unable to identify. Supporting this hypothesis, our series presented some peculiar characteristics.

We observed a higher incidence of chorea (54%) compared with that reported in the literature (15–30%) [12]. Moreover, all patients with chorea had mild cardiac
involvement, clinically, echocardiographically or both, confirming that severe carditis is less likely to occur in patients with chorea [13].

Although rheumatic chorea generally subsides spontaneously within 2–6 months, pharmacological treatment is reserved for patients with severe chorea preventing independent ambulation, self-feeding or high caloric expenditure [13]. Several different agents have been used: carbamazepine, haloperidol and sodium valproate. The use of prednisone in severe chorea is supported by uncontrolled observations [14] and randomized controlled trials [15]. Paz et al. [15] demonstrated that chorea complete remission time was significantly shorter in the prednisone group compared with the placebo group.

Therefore, we decided to treat our patients with severe chorea with prednisone with a prompt resolution of symptoms in all patients except one. Nowadays, in our opinion, steroid therapy should be the first option for severe chorea, in order to shorten the duration of symptoms.

Regarding the incidence of carditis, our data are comparable with those reported from other authors: in our cohort, 77% of patients had carditis, half of them with only echocardiographic findings, that is similar to data coming from other outbreaks reporting a variable incidence of 50–91% of cases [4, 16]. The same course was also described for arthritis, which was present in 46% of our patients, in line with data from other outbreaks reporting arthritis in 24–68% of cases [17, 18].

In our series, 5 out of 13 patients affected by ARF had echocardiographic carditis with no auscultatory evidence (silent carditis): three patients with chorea and two with arthritis and at least two minor manifestations. All of them completely recovered from carditis within 1–4 months of follow-up.

Since 1995, Wilson and Neutze [6] supported the conclusion that pulsed and colour Doppler echocardiography provide certain and objective methods to detect a minor degree of pathological regurgitation in the absence of characteristic clinical signs. A careful evaluation of the 2D colour Doppler echocardiography, with particular attention to differential diagnosis between pathological and physiological valvular regurgitation is recommended. In fact, subclinical or silent carditis is widely accepted as part of the spectrum of rheumatic carditis and several authors suggest considering it as a major or minor criterion of ARF [19, 20, 21, 23]. However, it has not yet been endorsed by the American Heart Association as an update of the Jones criteria [7, 19, 20, 21].

Taking into account our experience, despite the small number of our patients, we think that early 2D colour Doppler echocardiography should be performed by an experienced cardiologist in any case of suspected or defined ARF and any regurgitant jet should be meticulously described according to the published recommendations [6, 19].

Echocardiographic evaluation not only prevents clinical overdiagnosis, but also identifies those subclinical cases of carditis that would otherwise pass undiagnosed without receiving the correct prophylaxis [22]. In line with several authors [19, 20, 21, 23], we believe that echocardiography plays an important role in the early detection of silent carditis.

Whether subclinical rheumatic valvular damage has a different prognosis from clinical carditis is unknown. However, some studies demonstrate persistence of valve lesions in a number of patients with silent carditis in up to 8 years follow-up [24, 25], emphasizing that subclinical lesions are not necessarily transient and could sometimes even worsen [26].

Further prospective randomized studies are necessary to adequately establish the therapeutic and prognostic importance of valvular regurgitation detected by echocardiography.

Meanwhile, in our opinion, in a patient strongly suspected of ARF with silent carditis, proper secondary prophylaxis should be recommended in order to avoid the risk of additional cardiac damage, even if no data exist on prophylaxis duration. In fact, in our two cases that did not fulfill ARF criteria, we decided to start secondary prophylaxis as well, and to continue it for at least 10 years, as for rheumatic fever with carditis without residual heart disease according to the recommendations of the American Heart Association [9].

Moreover, it is well known that anyone who manifests carditis as an initial episode of ARF signal presents a relatively high risk for having carditis with recurrences. This problem particularly concerns the developing countries where morbidity and mortality due to ARF remain very high [27].

In conclusion, therefore, clinicians should be aware of, recognize and promptly treat bacterial acute pharyngitis, consider ARF diagnosis and carry out electrocardiographic investigation of all suspected patients even in developed countries.

**Rheumatology key messages**

- Early echocardiography should be performed by an experienced cardiologist in suspected or defined ARF.
- Echocardiography identifies those subclinical cases of carditis (silent carditis) that would otherwise pass undiagnosed.
- For silent carditis, prophylaxis should be continued for 10 years as for ARF with carditis without residual heart disease.

**Disclosure statement:** The authors have declared no conflicts of interest.

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