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Clinical and laboratory features of acute rheumatic fever from 18 years of experience

Caratteristiche cliniche e di laboratorio della febbre reumatica acuta: 18 anni di esperienza

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INTRODUCTION

Acute rheumatic fever (ARF) is a delayed, non-suppurative sequela of upper respiratory infection by group A streptococci, the main cause of heart disease in children and exceptionally in adults [1, 2]. In prospective studies of primary and recurrent ARF, cases of this disease occur only after a streptococcal infection. Acute rheumatic fever is most frequent among children belonging to the 6- to 15-year-old group [3, 4].

Indeed, its relative rarity in infants and in preschool age children has led some observers to question whether repeated "primary" infections might be a prerequisite for the development of this disease. Both initial and recurrent episodes also occur in adults. There is no clear-cut sex predilection, although there is a female preponderance in certain clinical manifestations, notably mitral stenosis and Sydenham's chorea when the latter occurs after puberty. In temperate climates rheumatic fever tends to occur less frequently in summer.

World Health Organization survey carried out between 1986 and 1990 estimated the prevalence of rheumatic fever–rheumatic heart disease per 1000 schoolchildren to be 12.6 in Zambia, 10.2 in Sudan, and 7.9 in Bolivia [5].

The incidence of ARF in western countries cannot be accurately determined due to difficulties in diagnosing the disease and to the lack of a rheumatic fever registry. As a consequence, it has been estimated at only 0.5 per 100,000 schoolchildren per year due to better environmental conditions rather than to large antibiotic usage [6, 7].

Therapy in ARF aims to quieten inflammation, to decrease fever and toxicity, and to control cardiac failure. The mainstays of treatment are salicylates and corticosteroids. These allow complete expression of the clinical manifestations to aid in diagnosis and also avoids post-therapeutic rebounds. Most patients require salicylates.

The most potent anti-inflammatory action of corticosteroids should be introduced when salicylates fail to control the inflammatory process or when carditis with congestive heart failure is present. ARF patients with positive throat cultures for group A streptococci should receive therapy with preferably penicillin G benzathine [8, 9].

The prognosis in rheumatic patients has been greatly improved by our ability to prevent recurrent attacks with their concomitant threat of additional myocardial and valvular damage. Rheumatic patients are at high risk of developing recurrent ARF after streptococcal upper respiratory infections. They need continuous prophylaxis in order to prevent recurrent streptococcal infections.

The recommended regimen for most patients in the United States and in other countries where ARF incidence is low consists of a single intramuscular injection of 1.2 million units of penicillin G benzathine to be provided every 4 weeks [8]. In the most comprehensive study re-

ported to date, children following such a regimen experienced a rheumatic fever recurrence rate of only 0.4 per 100 patient-years of observation.
Besides prevention from ARF recurrences, patients with residual rheumatic valvular disease must be protected from bacterial endocarditis whenever they undergo dental or surgical procedures that consistently evoke bacteremia or are known to be associated with the development of endocarditis [10].
The criteria (Jones, 1993) for diagnosis are well known but might be missed if inappropriate investigations are carried out during the acute illness. Those who have suffered an ARF attack are particularly predisposed to recurrent episodes after subsequent group A streptococcal infections. Continuous antimicrobial prophylaxis can prevent recurrent streptococcal infections and also ARF recurrences in rheumatic patients. An analysis of 30 cases of ARF observed in A.O. Ospedali Riuniti di Bergamo, Italy, follows hereafter to evaluate clinical and laboratory features.

PATIENTS AND METHODS

Clinical reports of all 30 patients admitted to Infectious Disease Department during 17 years (February 1986-June 2004) were retrospectively examined. In these patients ARF was diagnosed according to the Jones criteria, revised by the American Heart Association [11, 12].
Anamnestic data, clinical manifestations and laboratory results of all patients were evaluated. Cardiac function was studied and echocardiographic examination was performed: severe carditis was defined when the heart ejection fraction (EF) was less than 30%. Importantly, such instrumental investigations have changed little in time although their performance has meanwhile improved [13, 14].
In our study, throat swabs were sent to the Microbiology Institute for the culture of group A *Streptococcus* and incubated on blood agar with bacitracin disk for 18-24 h in an anaerobic atmosphere. The colonies with beta-haemolysis and possibly sensitive to the bacitracin test were isolated on blood agar and then identified by serological reaction. In vitro susceptibility tests were performed by disk diffusion for penicillin, ampicillin, erythromycin and clindamycin according to NCCLS [15, 16]. Statistical analysis was made by the Chi Square and Fisher Exact tests by Epi Info-Public Domain Software for Epidemiology and Disease Surveillance-CDC.

RESULTS

Thirty patients were retrospectively evaluated, 17 females (57%) and 13 males (43%), age range 9-66 years; 11 patients were aged under 18 (37%), an average of 13 for male and 11 for female, while 19 patients were aged over 18 (63%), an average of 40 for male and 34 for female. Given the long time considered for this study we decided to divide it into two periods: 1986-1995 and 1995-2004.
Importantly, these two periods consisted respectively of 22 and 8 patients.

Table 1 - Clinical laboratory results.

Patient	S. pyogenes	*ASL*	*ESR*
1	Neg	1037	90
2	Neg	595	81
3	Neg	600	75
4	Neg	600	54
5	Neg	340	44
6	Neg	1200	89
7	Neg	400	68
8	Pos	1162	80
9	Neg	1875	100
10	Neg	400	124
11	Pos (blood)	900	64
12	Not done	600	70
13	Neg	1200	115
14	Pos	800	95
15	Pos	400	108
16	Neg	809	100
17	Neg	2510	90
18	Pos	250	94
19	Neg	400	61
20	Neg	1600	77
21	Neg	800	55
22	Neg	914	126
23	Neg	1260	44
24	Pos	1596	100
25	Not done	300	35
26	Pos	1200	51
27	Neg	800	90
28	Neg	1290	100
29	Pos	565	54
30	Neg	331	45

Table 2 - Cardiac features of patients.

Pt.	*Gender*	*Carditis*	*Abnormal ECG*	*Complicance valvue*	*Therapy*
1	F	17 NO	NO	cured	ASA
2	F	33 NO	Atrioventricular block 1°	cured	ASA
3	F	28 pancarditis	Atrioventricular block 1°	mitral insufficiency	ASA + steroid
4	F	25 NO	NO	cured	ASA
5	M	36 NO	NO	cured	ASA
6	M	9 pancarditis	NO	cured	ASA
7	M	9 NO	NO	cured	ASA
8	M	28 NO	NO	cured	ASA
9	F	43 pancarditis	Aspecific	cured	ASA
10	M	11 pancarditis	Aspecific	mitral-aortic insufficiency*	ASA + steroid
11	M	66 pancarditis	NO	cured	ASA + steroid
12	F	14 pancarditis	Aspecific	mitral-aortic insufficiency*	ASA
13	M	33 NO	NO	cured	ASA + steroid
14	M	20 NO	Atrioventricular block 1°	cured	ASA
15	F	13 NO	NO	cured	ASA
16	M	54 pancarditis	NO	cured	ASA
17	F	27 NO	ventricular-extrasystole	cured	ASA
18	F	27 NO	Atrioventricular block 1°	cured	ASA
19	F	13 pancarditis	NO	mitral insufficiency	ASA
20	F	17 pancarditis	NO	mitral insufficiency	ASA
21	M	13 pancarditis	Aspecific	mitral-aortic insufficiency*	ASA
22	F	33 NO	NO	cured	ASA
23	F	26 pancarditis	Atrioventricular block 1°	mitral insufficiency	ASA + steroid
24	F	26 pancarditis	Aspecific	mitral-aortic insufficiency*	ASA
25	M	46 pancarditis	Aspecific	mitral-aortic insufficiency*	ASA + steroid
26	M	11 pancarditis	atrial-extrasystole	cured	ASA
27	F	15 pancarditis	Atrioventricular block 1°	cured	ASA + steroid
28	F	30 NO	NO	cured	ASA + steroid
29	M	38 NO	NO	cured	ASA + steroid
30	F	29 NO	NO	cured	ASA + steroid

*Cardio-surgical valves replacement.

The overall average recovery period was 18 days, within a range of 5-55 days. On a two-period basis, the first amounts to 20 days and the second to 12 days, with a 40% reduction in the average recovery period and without any difference between the various age groups ($p = 0.09$). Twenty-seven percent of patients presented more than one episode. If we evaluate the two periods separately we note that the subjects with more than one episode rises to 32% in the first period and decreases to 12% in the second, which is a significant difference ($p = 0.02$). On shifting, instead, the evaluation criteria to patients of the same age class (over 18) there is a great difference ($p = 0.01$) between the first period (45%) and the second (13%).

At recovery 29/30 patients presented fever (97%), 26 arthritis (86%), 22 angina (73%), 3 erythema marginatum (10%), 1 chorea (3%) and 15 carditis (50%) subdivided into 54% for the first period and 12% for the second in the same age class (over 18) ($p < 0.05$). First degree atrio-ventricular block was observed in 6 patients (20%), atrial and ventricular escape in 2 patients (7%). Throat cultures were positive for group A *Streptococcus* in 8 tested patients (27%) and all susceptible to macrolides; one of them had received correct antimicrobial treatment before hospitalization while 11/30 (37%) patients had not been treated at home; the remaining 18/30 had received adequate antibiotics only for a short time or incorrectly (therapy).

Twenty-six patients (87%) showed anti-streptolysin O antibodies (ASL) titres ≥400 UI/l dur-

ing hospitalization and the Erythrocyte Sedimentation Rate (ESR) was ≥35 mm/h in all patients (100%) (Table 1).
Of the 15 patients with carditis, 9 (60%) had mild to moderate heart disease, 4 had long-term sequelae and mild mitral regurgitation but no sign of heart failure, 6 (40%) had severe carditis with serious damage and severe mitro-aortic insufficiency. Of the latter, 5 had valve replacement operations using mechanical prosthesis (Table 2). Severe carditis associated to a later ARF diagnosis were observed. ARF was diagnosed in 10 patients (33%) during April-May and 12 (40%) during October-March, confirming ARF as a seasonal disease.
Eight patients with recurrent disease had been administered secondary antibiotic prophylaxis according to international protocols. All 30 patients were cured by ASA and 33% ASA + steroid and observed by a follow-up period of 48 months with a favourable evolution. For an overview of the results, see Tables 1 and 2.

DISCUSSION

Rheumatic disease is found world-wide. It is always preceded by streptococcal pharyngitis which can be asymptomatic in 25-30% cases. People belonging to lower socio-economic classes, children and recruits are those most affected. In our patients the incidence of ARF in the paediatric population has significantly decreased in recent years.
Pathogenesis of ARF is complex and may depend on a number of microbial and host factors, particularly autoimmune responses against host tissues [17]. Diagnosis of rheumatic disease must be done only after immunological evidence of recent streptococcal infection. The most widely used standardized test is the determination of anti-streptolysin O titres, as our experience also confirmed. No changes in laboratory and microbiological tests have been recently introduced. Echocardiographic investigations have not changed in time though their performance has recently improved.
Interestingly, mean recovery presents no significant difference when the same age group (over 18) is considered. This is an aspect that would deserve further investigation.
The significant difference in patients who have more than one episode of ARF, in the two periods considered, is certainly due to the secondary prophylaxis by antibiotics that was applied more rigorously according to national and international guidelines [8, 9].
Carditis is reported to occur in 50% of patients with ARF; furthermore, our data indicate that rheumatic heart disease may determine permanent and/or potentially life-threatening heart damage, requiring cardiac surgery: 5 out of 28 patients had a valve replacement due to mitro-aortic insufficiency. In recent years the incidence of carditis has dramatically diminished since the patients were cured adequately and early on. Adequate anti-streptococcal treatment is decisive in acute rheumatic fever development and macrolide-resistance which has recently grown up to 30% in our countrly should be always taken into account for its treatment or reduction in ARF incidence in all western countries over the last few decades has paradoxically brought to its under-consideration as a differential diagnosis.
Our 18-year series confirms that it is not possible to declare ARF a historical disease.

Key words: rheumatic fever, heart disease, carditis and group A *Streptococcus*

SUMMARY

We present the retrospective analysis of clinical manifestations and laboratory findings observed in 30 patients (M/F 13/17; age range 9-66 yrs) affected by acute rheumatic fever observed within the Infectious Disease Department during a period of 18 years (1986-2004). Carditis was diagnosed on clinical and echocardiographic grounds and occurred in 50% of patients. These patients presented mild to moderate heart disease (30%) and severe carditis (20%). Our data confirm that rheumatic cardiac disease could determine permanent and/or severe heart damage. All patients were observed during a 48-month period of follow-up without exitus.

RIASSUNTO

Nel presente lavoro è presentata l'analisi retrospettiva delle manifestazioni cliniche e dei risultati di laboratorio osservati in 30 pazienti, M/F 13/17, età range 9-66 anni, affetti da febbre reumatica acuta, osservati presso l'Unità Operativa di Malattie Infettive in un periodo di 18 anni (1986-2004). La diagnosi di cardite è stata posta su base clinica ed ecocardiografica, ha interessato il 50% dei pazienti che hanno presentato un coinvolgimento cardiaco da lieve a moderato nel 30% ed una grave cardite nel 20% di questi. I nostri dati confermano che la malattia reumatica può determinare un danno cardiaco permanente e/o grave. Tutti i pazienti sono stati seguiti con un follow-up di almeno 48 mesi senza eventi fatali.

REFERENCES

[1] Rullan E., Sigal L.H. Rheumatic fever. *Curr Rheumatol Rep*. 3, 445-452, 2001.

[2] McDonald M., Currie B.J., Carapetis J.R. Acute rheumatic fever: a chink in the chain that links the heart to the throat. *Lancet Infect Dis*. 4, 240-245, 2004.

[3] Cunningham M.W. Pathogenesis of group A streptococcal infections. *Clin Microbiol Rev.* 13, 470-511, 2000.

[4] Tani L.Y., Veasy L.G., Minich L.L., Shaddy R.E. Rheumatic fever in children younger than 5 years: is the presentation different? *Pediatrics* 112, 1065-1068, 2003.

[5] World Health Organization. WHO programme for the prevention of rheumatic fever/rheumatic heart disease in 16 developing countries: Report from Phase I (1986-90). Bull WHO. 1992; 70: 213-218.

[6] Stollerman G.H. The changing face of rheumatic fever in the 20th century. *J Med Microbiol.* 47, 655-657, 1998.

[7] Stollerman G.H. Current issues in the prevention of rheumatic fever. *Minerva Med.* 93, 371-387, 2002.

[8] Cilliers A.M., Manyemba J., Saloojee H. Anti-inflammatory treatment for carditis in acute rheumatic fever. *Cochrane Database Syst. Rev*. CD003176, 2003.

[9] Nalk N., Bahl V.K. Acute Rheumatic fever: whither steroids? *Indian Heart J*. 54, 363-367, 2002.

[10] Stollerman G.H. Rheumatic fever in the 21st century. *Clin Infect Dis*. 33, 806-814, 2001.

[11] American Heart Association: Jones criteria (revised) for guidance in the diagnosis of rheumatic fever. *Circulation.* 69, 204a, 1984.

[12] Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 1992 update. Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease Council on Cardiovascular Disease in the Young, the American Heart Association. *JAMA.* 268, 2069-2073, 1992.

[13] Vasan R.S., Shrivastava S., Vijayakumar M.D. Echocardiographic evaluation of patients with acute rheumatic fever and rheumatic carditis. *Circulation.* 94, 73-82, 1996.

[14] Mota C.C. Doppler echocardiographic assessment of subclinical valvitis in the gnosis of acute rheumatic fever. *Cardiol Young*. 11, 251-254, 2001.

[15] Ruoff K.L. Streptococcus. *Manual of Clinical Microbiology, ed. 8*. Murray PR. 2003. Washington, D.C.

[16] American Society for Microbiology, NCCLS. Performance Standards for antimicrobial susceptibility testing. M 100-S14, vol. 24, 2004.

[17] Guilherme L., Kalil J. Rheumatic fever: from sore throat to autoimmune heart lesions. *Int Arch Allergy Immunol*. 134, 56-64, 2004.