EXTENDED REPORTS

A clinical and serological comparison of group A versus non-group A streptococcal reactive arthritis and throat culture negative cases of post-streptococcal reactive arthritis

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Abstract

Objective—To identify clinical and serological differences of patients with reactive arthritis after infection with Lancefield group A β -haemolytic streptococci (GAS), compared with non-group A—that is, group C or G streptococci (NGAS:GCS/GGS), and a group of culture negative or unidentified streptococci (GUS).

Methods—A prospective study of consecutive patients with reactive arthritis after serologically or culture confirmed infection with β -haemolytic streptococci, presenting to the outpatient department of rheumatology from January 1992 until January 1998. Alternative causes for reactive arthritis were excluded. Main outcome measures were clinical and serological characteristics including antistreptolysine-O (ASO) and anti-deoxyribonuclease-B (antiDNase-B) antibody titres.

Results—41 patients (female/male ratio 22/19; mean (SD) age 38 (13) years) with reactive arthritis were included. Culture of throat swab was positive in 13 cases (32%): 6 (15%) GAS, 7 NGAS (17%), that is, 5 (12%) GCS, 2 (5%) GGS. In 28 cases throat culture remained negative resulting in a group of unidentified streptococci; antibiotic pre-treatment had been given by the general practitioner in 18 cases (64%). Arthritis was non-migratory, the number of arthritic joints in GAS and NGAS was similar, whereas in NGAS patients fewer joints were involved than in GUS: mean (SEM) 36 swollen joint index: 3.3 (1.0) in NGAS *v* 5.6 (1.0) in GUS ($p < 0.005$); 28 swollen joint index: 2.9 (1.0) in NGAS *v* 4.3 (0.8) in GUS ($p < 0.05$). Extra-articular manifestations—that is, erythema nodosum/ multiforme, AV conduction block or hepatitis—were observed after GAS or GUS infection, but not after NGAS infection. ASO and/or antiDNase-B rose significantly in all patients. The maximal titres for ASO and antiDNase-B in 41 PSRA patients were: mean (SEM) 1242 (232) U/l and 890 (100) U/l

respectively; the maximal ASO titres were similar in the three groups: mean (SEM) 1125 (185) in GAS, 625 (160) in NGAS (GAS *v* NGAS: $p = 0.17$), and 1430 (320) U/l in GUS (NGAS *v* GUS: $p = 0.10$). AntiDNase-B titres were: mean (SEM) 1075 (180) in GAS, 375 (105) in NGAS (GAS *v* NGAS: $p < 0.01$), and 995 (125) U/l in GUS (NGAS *v* GUS: $p < 0.005$). ASO: antiDNase-B ratios were: mean (SEM) 0.89 (0.21) in GAS, 2.60 (0.76) in NGAS (GAS *v* NGAS: $p < 0.05$), and 1.43 (0.28) in GUS (NGAS *v* GUS: $p = 0.12$).

Conclusion—Post-streptococcal reactive arthritis occurs not infrequently. Differentiation of PSRA based on the causative streptococcal strain is frequently thwarted by negative throat cultures. Sometimes extra-articular manifestations are present that exclude NGAS as the causative organism. Serologically, lower antiDNase-B titres may be indicative for primary NGAS infection; the ASO/antiDNase-B ratio may be of additive value for differentiation in cases of a negative throat culture: the higher ASO/antiDNase-B ratios suggesting primary NGAS infection. In reactive arthritis, serological monitoring consisting of a simultaneous titration of antiDNase-B and ASO, seems to be of clinical importance to trace GAS induced cases, especially when throat cultures remain negative.

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During the past decennium the non-suppurative sequelae of infections with β -haemolytic streptococci are being encountered more frequently. A migrating polyarthritis after throat infection with group A β -haemolytic streptococci (GAS) is classically attributed to acute rheumatic fever (ARF).¹ In addition, sterile non-migratory arthritis may occur as a separate entity, the so called post-streptococcal reactive arthritis (PSRA).²⁻⁶ PSRA may develop after primary GAS throat infection,²⁻⁴ but also after infection with the non-group A streptococci (NGAS): group C

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Table 1 Demographic data of present group of PSRA patients (n=41)

Throat culture	positive	positive	negative
Lancefield group	A	C/G	undetermined
abbreviation used	GAS	GCS/GGS NGAS	GUS
Patient number	6	7	28
f:m ratio	3:3	2:5	17:11
Streptococcal infection in the past:			
pneumonia/pharyngitis	2	0	0
post-streptococcal sequelae in the past:			
PSRA	0	1	0
Age (y) (SD)	32 (8)	28 (8)*	43 (12)

Statistical group comparisons: NGAS v GUS: *p<0.05. Insignificant p values are not demonstrated.

(GCS) or group G streptococci (GGS).⁵⁻⁷⁻¹⁰ To establish the diagnosis ARF or PSRA it is necessary to record evidence of a recent streptococcal infection by throat culture or increasing anti-streptococcal antibodies.¹¹ Because the throat culture provides evidence of a preceding streptococcal infection in only a minority of the patients,¹²⁻¹³ the determination of anti-streptococcal antibodies is of greater importance. In ARF about 80% of patients have an increased anti-streptolysine-O (ASO) titre. When two or more assays are used, for example, ASO, anti-deoxyribonuclease-B, antihyaluronidase, at least 95% of patients with ARF show a rise in at least one of the antibodies.¹¹ A differentiation based on the primary causative streptococcal strain is of importance because only GAS infections may be associated with a devastating carditis, a major feature of ARF, which is rightly feared. As the antigenic features of several streptococcal strains may differ, we hypothesised that clinical parameters as well as in vivo antibody responses might also differ. We prospectively studied whether clinical parameters and antibody responses—that is, ASO and antideoxyribonuclease-B (antiDNase-B)—may help to differentiate between cases occurring secondary to GAS and those secondary to NGAS (GCS/GGS).

Methods

STUDY DESIGN

The cohort comprised consecutive patients older than 10 years of age, with arthritis secondary to a serologically or culture verified infection with β -haemolytic streptococci, presenting in our outpatient clinics of rheumatology from January 1992 until January 1998. Before inclusion, other causes of arthritis were excluded: septic arthritis, rheumatoid arthritis, connective tissue disease, crystal deposition disease, reactive arthritis (attributable to parvovirus B19, salmonella, shigella, campylobacter, and chlamydia, gonococci and spirochetes), and arthritis secondary to inflammatory bowel disease. All patients were regularly seen on outpatient basis for follow up. The following laboratory tests were obtained: full blood count, erythrocyte sedimentation rate, serum creatinine, alkaline phosphatase, γ -glutamyltransferase, aspartate aminotransferase, alanine aminotransferase, uric acid, IgM rheumatoid factor, antinuclear antibodies, C reactive protein and urine microscopy. An electrocardiogram was made of all patients. An echocardiogram was obtained in cases with a cardiac murmur or with a conduction block on the electrocardiogram.

The numbers of joints involved were counted according to the 36 swollen joint index (SJI), and the 28 SJI.¹⁴

SEROLOGICAL MEASUREMENTS

In all patients ASO and antiDNase-B titres were simultaneously measured and sequentially monitored at time points 2, 3, 4, 6, 8, 12 weeks after the primary throat infection and where applicable also at 16 and 24 weeks. To meet the criteria for a serologically confirmed streptococcal infection, specific features of the ASO and antiDNase-B titres were required: (1) ASO > 200 U/l in adults, ASO >300 U/l in adolescents; anti-DNase-B > 200 U/l irrespective of age, and (2) one or both titres must show a significant rise: critical difference between consecutive ASO values 26% and between consecutive antiDNase-B values 14%. Serological titres were determined by a nephelometry kit from Behring (Marburg, Germany). Patients were subdivided into three groups, based on the bacteriological result from the throat culture: group A streptococci (GAS), non-group A streptococci (NGAS)—that is, group C or G streptococci (GCS/GGS)—and a group of unidentified streptococci (GUS).

STATISTICAL TESTS

Intergroup comparison was done of GAS versus NGAS (GCS/GGS) and NGAS versus GUS groups. In 2 $\times$ 2 tables, Fisher's exact test was applied because of small numbers in the expected area. Unpaired Student's *t* test was used for comparison of SJI. Mann-Whitney's two sample test was used for comparison of biochemical and serological data. *p* Values <0.05 were considered statistically significant (two tailed).

Results

During a period of six years 41 patients (female/male ratio 22/19; mean (SD) age 38 (13) year with sterile arthritis secondary to streptococcal infection presented in our outpatient clinic. All cases were sporadic, and clustering of cases was not encountered. Table 1 gives demographic data of patient groups. Table 2 gives the clinical data. After an interval of approximately three weeks all patients presented with arthritis, which was confirmed at physical examination by one of the authors. Before arthritis the majority of patients (61%) had complained of a painful throat. Antibiotic pre-treatment had been given by the general practitioner to one of six (17%) GAS, one of seven (14%) NGAS, and 18 of 28 (64%) GUS patients. Throat swab culture was positive in 13 of 41 patients (32%), especially 12 patients without previous antibiotic treatment and in patients younger than 40 years of age (culture positive <40 years: 12 patients; culture negative <40 years: 14 patients; culture positive >40 years: one patient; culture negative >40 years: 14 patients; odds ratio 7.3). In patients without previous antibiotic pre-treatment, throat culture became positive in 11 of 21 cases (52%); whereas in patients with antibiotic pre-treatment, throat culture became positive in

Table 2 Clinical data of present group of PSRA patients (n=41). Data are means (SEM), or numbers of patients (%)

Abbreviation used	GAS	NGAS	GUS
Patient number	6	7	28
Interval sore throat-arthritis (days)	35 (45)	25 (14)	17 (14)
Antibiotic pretreatment	1 (17%)†	1 (14%)‡	18 (68%)
Arthritis (number (%))			
monoarticular	3 (50%)	2 (29%)	6 (21%)
oligoarticular	1 (17%)	4 (57%)	12 (43%)
polyarticular	2 (33%)	1 (14%)	10 (36%)
Symmetrical joints disease	3 (50%)	1 (14%)	16 (57%)
Shoulder	0 (0%)	0 (0%)	1 (4%)
Elbow	2 (33%)	3 (43%)	7 (25%)
Wrist	1 (17%)	3 (43%)	14 (50%)
MCP	1 (17%)	4 (57%)	9 (32%)
PIP	2 (33%)	2 (29%)	7 (25%)
Knee	2 (33%)	5 (71%)	17 (61%)
Ankle	5 (83%)	3 (43%)	13 (46%)
MTP	1 (16%)	1 (14%)	4 (14%)
Extra-articular findings (number (%))			
carditis*	0	0	0
first degree AV block	1 (17%)	0	2 (7%)
hepatitis	1 (17%)	0	2 (7%)
erythema	2 (33%)	0	9 (32%)
nodosum	2 (33%)	0	5 (18%)
multiforme	0	0	4 (14%)
lobular panniculitis	0	0	1 (4%)
Recovery (days)	30 (16)	80 (60)	42 (40)

*Echocardiography was performed in two (33%) of GAS, one (14%) of NGAS, and three (11%) of GUS induced PSRA patients: all normal findings. Statistical group comparisons: GAS v GUS: †p<0.05; NGAS v GUS: ‡p<0.05; insignificant p values are not demonstrated.

Table 3 Comparison of laboratory and clinical data of PSRA patients (n=41) subdivided into three groups. Data are means (SEM)

Abbreviation used	GAS	NGAS	GUS
Patient number	6	7	28
ESR (mm 1st h) (normal <10 mm 1st h)	55 (14)	51 (13)	63 (6)
CRP (mg/l) (normal <9 mg/l)	50 (17)	41 (15)	67 (11)
Leucocyte count (×10 ⁹ /l)	10.4 (0.8)	10.2 (1.5)	10.1 (0.6)
ASO _{max} (U/l)	1125 (185)	625 (160)	1430 (320)
Anti-DNase-B _{max} (U/l)	1075 (180)**	375 (105)‡	995 (125)
ASO _{max} (anti-DNase-B _{max})	0.89 (0.21)*	2.60 (0.76)	1.43 (0.28)
Number of arthritic joints			
great joints	2.2 (1.0)	2.1 (0.7)	2.6 (0.3)
36 swollen joint index	3.5 (1.3)	3.3 (1.0)‡	5.6 (1.0)§
28 swollen joint index	1.8 (0.8)	2.9 (1.0)†	4.3 (0.8)

Statistical group comparisons: GAS v NGAS: *p<0.05, **p<0.01; NGAS v GUS: †p<0.05, ‡p<0.005; GAS vs GUS: §p<0.01, || p<0.005. Insignificant p values are not demonstrated.

Table 4 Comparison of throat culture negative cases of post-streptococcal reactive arthritis (GUS) without and with previous antibiotic treatment (n=28). Data are means (SEM)

	Without antibiotic pre-treatment (n=10)	With antibiotic pre-treatment (n=18)	Significance
36 SJI	4.5 (1.7)	6.3 (1.3)	NS
28 SJI	3.7 (1.6)	4.7 (1.0)	NS
Extra-articular manifestations (%)	60	44	NS
ESR (normal <10 mm 1st h)	66 (10)	62(8)	NS
CRP (normal <9 mg/l)	84 (20)	58(13)	NS
Leucocyte count (×10 ⁹ /l)	11.3 (2.0)	9.4 (0.9)	NS
ASO max (U/l)	1335 (445)	1480 (450)	NS
anti-DNase-B max (U/l)	1080 (280)	950 (125)	NS
ASO: anti-DNase-B ratio	1.07 (0.32)	1.64 (0.40)	NS
Recovery (days)	18 (5)	46 (9)	NS

Extra-articular manifestations are erythema nodosum, erythema multiforme, hepatitis or lobular panniculitis.

only two of 20 patients (10%): one each GAS and GCS; this difference was significant, p<0.001.

In the three groups there were similar frequencies of monoarticular, oligoarticular, and polyarticular presentations. The individual joint distribution was quite similar in the three groups. The arthritis was non-migratory in the majority of patients (96%) and it occurred symmetrically in 50% of the cases. In the NGAS induced cases no extra-articular manifestations were observed. In one third of the GAS and GUS group an erythema nodosum or

marginatum appeared. In two patients in the GUS, and in one patient in the GAS group a first degree atrioventricular conduction block occurred. Similar frequencies were seen with respect to the occurrence of “cholestatic” hepatitis. The SJIs were similar in GAS and NGAS. In NGAS patients significantly fewer joints were involved than in GUS: mean (SEM) 36 SJI 3.3 (1.0) in NGAS v 5.6 (1.0) in GUS (p<0.005); 28 SJI 2.9 (1.0) in NGAS v 4.3 (0.8) in GUS (p<0.05) (see table 3). A comparison of the SJIs in GUS v GAS showed that in GAS lower index scores were found than in GUS: mean (SEM) 36 SJI 3.5 (1.3) in GAS v 5.6 (1.0) in GUS (p<0.01); 28 SJI 1.8 (0.8) in GAS v 4.3 (0.8) in GUS (p<0.005).

All patients responded well to NSAID treatment (diclofenac 50 mg thrice daily, ibuprofen 400 mg thrice daily or naproxen 500 mg twice daily), which was given during a prolonged period. All patients recovered fully after approximately two months; see table 2. None of the patients had signs of acute glomerulonephritis.

In a small group of four patients (10%) a transient “cholestatic” hepatitis was seen: mean (SEM) alkaline phosphatase (normal: 30–105 U/l) 246 (36) U/l, γ-glutamyltransferase (normal: 9–50 U/l) 193 (32) U/l, aspartate aminotransferase (normal: 5–30 U/l) 71 (36) U/l, alanine aminotransferase (normal: 5–30 U/l) 111 (23) U/l. In one patient GAS had been cultured from the throat swab, but the others were in the GUS group.

A two year period of monthly penicillin prophylaxis was advised in the GAS and GUS group. Two patients from the GUS group refused to follow medical advice. In one of them PSRA recurred 15 months after the first episode. In the patients who were compliant with penicillin prophylaxis, no recurrence has yet been observed. So far 23 patients have uneventfully completed the two year period of prophylaxis. Total follow up after prophylaxis in these patients was 828 months. During this period no recurrences of arthritis nor of other sequelae secondary to streptococcal infection have been observed.

Carditis could not be detected in the present groups of PSRA patients. A search of similar age groups in our hospital diagnosis registration system showed that during the study period no patients with ARF were referred to other specialists such as cardiologists and paediatricians.

Table 3 gives laboratory and serological data. At presentation the erythrocyte sedimentation rate (ESR), and the C reactive protein (CRP) had increased in all groups similarly. In the GAS, GCS/GGS, and GUS groups leucocytosis occurred in 67%, 43%, and 52% respectively, resulting in a similar mean value.

Table 4 compares patients without (n=10) and with (n=18) previous antibiotic treatment in the throat culture negative group (n=28). We found no differences between the two groups in the number of swollen joints, extra-articular manifestations, acute phase response, anti-streptococcal antibody response or time of recovery.

Figure 1 Antibody titres of ASO in the GAS ($n=6$), NGAS ($n=7$), and GUS induced ($n=28$) PSRA patients from week 2–24 after streptococcal throat infection. Data are means (SEM).

Figure 2 Antibody titres of antiDNase-B in the GAS- ($n=6$), NGAS ($n=7$), and GUS induced ($n=28$) PSRA patients from week 2–24 after streptococcal throat infection. Data are means (SEM).

Figure 3 ASO:antiDNase B ratio in the GAS ($n=6$), NGAS ($n=7$), and GUS induced ($n=28$) PSRA patients. Data are means (SEM).

Figures 1 and 2 show the initial increase followed by a decrease in both the titres of ASO and antiDNase-B, respectively. The time courses of the titre curves for ASO and antiDNase-B were similar in the GAS and GUS groups. After NGAS infection, the ASO titre curve was less prominent (GAS *v* NGAS: $p<0.05$; repeated measures analysis of variance), and the antiDNase-B titre curve remained almost flat during the first eight weeks (GAS *v* NGAS: $p<0.0005$; repeated measures analysis of variance).

Possibly because of the low number of patients, the mean maximal ASO titre (SEM)

in GAS patients tended to be only slightly higher than in NGAS patients (GAS *v* NGAS: $p=0.17$). Even in the GUS patients, which were the majority, the mean maximal ASO titre was not significantly different from that of NGAS patients ($p=0.10$). In contrast with the ASO titres, the antiDNase-B titres differed significantly between the three groups: the maximum antiDNase-B titres were higher in the GAS and the GUS patients than in NGAS patients: GAS *v* NGAS: $p<0.01$, and GUS *v* NGAS: $p<0.005$.

Indeed, the ASO antiDNase-B ratio was significantly lower in the GAS patients when compared with the NGAS patients: 0.89 *v* 2.60 ; $p<0.05$. The ratio was insignificantly ($p=0.12$) lower in the GUS patients than in the NGAS patients (fig 3).

Discussion

One of the most feared sequelae to GAS infection is ARF, in particular carditis. For several decades, however, its frequency has declined enormously. In the past decennium, the post-streptococcal diseases, including PSRA have emerged.¹⁵ The aim of this study is to find clinical, biochemical or serological parameters that enable us to differentiate between the different streptococcal strains. This is of importance because only GAS infections can be associated with devastating carditis, and thus require antibiotic prophylaxis.

The arthritis indices, as measured by the 36 and 28 SJIs, showed that the number of joints involved in NGAS was lower than in GUS. Remarkably, the SJIs in GAS and NGAS were similar; this may be related to a possibly coincidentally high number of monoarthritis patients in the GAS group. The distribution of affected joints in the three group was the same. Clinically, several additional findings may help in the differentiation of GAS and NGAS induced PSRA. An argument that in PSRA, GAS is the responsible infection, may be deduced from the occurrence in reactive arthritis of atrioventricular conduction block, of dermatitis—that is, erythema nodosum/multiforme, and of “cholestatic” hepatitis. In the past, erythema nodosum was rarely seen in ARF patients,^{13 16 17} occurrence 4–7%.¹³ In the presented GAS and GUS induced PSRA patients, erythema nodosum and/or multiforme were observed in respectively 33% and 32%. Interestingly, these erythemas were not found in NGAS induced PSRA patients. In addition to the arthritis, some GAS and GUS induced PSRA patients had “cholestatic” hepatitis with piecemeal necrosis, which has only been sporadically described in ARF.^{18 19} The presence of these extra-articular phenomena provides an argument for primary GAS infection. Further studies into possible immunological explanations are warranted. The group of throat culture negative patients (GUS) has the largest number of patients and probably contains a mixture of group A, non-group A and possibly other streptococcal infections. In this group of patients, antibiotic treatment before the outbreak of arthritis does not eradicate the possibility of PSRA.

Moreover the PSRA seemed to be just as aggressive as that seen in the group where throat swabs were positive. However, we do not know how many cases of PSRA can be prevented by very early antibiotic treatment of streptococcal pharyngotonsillitis. To answer this question another study design is needed.

A (semi)recent streptococcal infection can only be diagnosed, by a combination of a rise and subsequent fall in streptococcal antibody titre(s). The ultimate proof that pharyngitis is caused by β -haemolytic streptococci, either by GAS or by NGAS, must come from throat culture. Not infrequently, however, throat culture remains negative. Studies have shown that in adults about 20% of cases with streptococcal throat infection may be caused by NGAS—that is, GCS and GGS.^{5, 20} Our study found a positive throat culture in PSRA patients in approximately 30% of cases, a figure that concurs with other studies. The percentage of positive throat cultures was higher, approximately 50% in this study, if patients had not had previous antibiotic treatment. We found six GAS positive throat cultures, but in only two of these could the exact M-serotype be determined: M-serotype 9 and 28. They have not previously been reported to be either nephritogenic, or associated with ARF.¹⁵ The identification of further arthritogenic strains can only be achieved by M-serotyping of streptococcal throat infections. The pathogenic link of certain antigenic (dis)similarities between GCS/GGS and some GAS strains, explaining (dis)similarities in clinical outcome measures, remains speculative.

Markers enabling differentiation of streptococcal strains may be found in serological antibody responses, as different streptococcal strains are known to exhibit different antigenic epitopes. In vitro, streptolysin-O is produced by most strains of GAS, but also by some strains of GCS/GGS. In vitro, ASO antibody titres could not discriminate between the primary causative streptococcal strains, GAS and NGAS. Furthermore, most GAS strains produce, in vitro, significant amounts of the exoenzyme DNase-B, whereas GCS and GGS produce lower amounts of Dnase-B.² This, combined with possibly lower microbial virulence, may explain that the in vivo antibody response measured by antiDNase-B may be poor after GCS and GGS infection. These factors explain that serological confirmation can be troublesome after primary NGAS infection. As the antigenic armature of different sub-

groups of β -haemolytic streptococci may differ, we hypothesised that ASO antiDNase-B ratios might help in the differentiation of streptococcal strains in PSRA, particularly when throat culture remains negative. Our data show that the combined use of ASO and antiDNase-B, such as in a ratio of ASO antiDNase-B, may be of valuable help in the serological differentiation of the three groups. Higher ratios were suggestive of NGAS infection; this may well be a useful clinical tool in helping decide whether penicillin prophylaxis should or should not be considered.

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