Annals of the Rheumatic Diseases, 1985, **44**, 399–405

Triggering infections in reactive arthritis

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SUMMARY Certain microbes like yersinia, salmonella, shigella, campylobacter, chlamydia, and possibly gonococcus can trigger reactive arthritis especially in patients of the HLA-B27 type. In the present study we have used serological and culture methods to identify the probable triggering infection in 50 consecutive HLA-B27 positive patients diagnosed as having reactive arthritis. The two most common triggering agents thus identified were *Yersinia enterocolitica* (12 patients) and *Chlamydia trachomatis* (11 patients). In addition six patients had high antistreptolysin O titres and two high teichoic acid antibody titres suggesting group A streptococci and *Staphylococcus aureus* as triggering agents. In 13 patients no preceding infection could be identified. The identity of the infective agent seems to have very little effect on the clinical picture of the reactive arthritis – the only difference between the various aetiological groups in the present material was absence of fever in the patients with a preceding *C. trachomatis* infection, of whom only one out of 11 had a temperature $\geq$ 38°C, whereas 13 of 16 patients with a preceding enterobacterial, and five of the eight patients with a streptococcal or staphylococcal infection had raised temperatures.

Key words: infectious, yersinia, chlamydia, HLA antigens.

Certain gastrointestinal and genitourinary tract infections can trigger reactive arthritis especially in patients with the histocompatibility antigen HLA-B27.[1] The best known triggering agents are yersinia,[2] salmonella,[3 4] shigella,[5] campylobacter,[6 7] chlamydia,[8 9] and gonococcus.[10] Complete or incomplete Reiter's syndrome is observed in one-third of patients with yersinia arthritis and in most of those with salmonella arthritis.[11] Rheumatic fever is another form of reactive arthritis; it is triggered by a pharyngeal infection caused by group A streptococci and is not linked to HLA-B27.[12]

The pathogenesis of reactive arthritis is poorly understood. The clinical picture of yersinia arthritis is somewhat modified by the genetics of the patient so that joint symptoms are more severe in HLA-B27 positive than negative patients.[11 13] Iritis, conjunctivitis, carditis, urological symptoms, and back pain occur mainly in the HLA-B27 positive group, whereas erythema nodosum is more common among HLA-B27 negative patients.

In the present study we have applied a wide set of serological assays and microbiological culture methods in an attempt to identify the triggering infections in 50 consecutive patients whose clinical picture was compatible with reactive arthritis and who were HLA-B27 positive. This allowed us to define the most common triggering infections and to test whether and in which way the clinical picture of the developing arthritis was influenced by the different triggering agents.

Accepted for publication 4 December 1984.
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Patients and methods

PATIENTS

Fifty consecutive patients from the Helsinki Uni-

versity Central Hospital were studied during 1978–80 on the basis of the following criteria: (1) the clinical picture was compatible with reactive arthritis; (2) the duration of joint symptoms had been less than two months; (3) the patient was HLA-B27 positive.

The patients were followed for a minimum of six months or until all the joint symptoms had disappeared. Careful clinical and rheumatological examination was performed once a month, and at each examination a serum sample was drawn for the serological assays. Special attention was focused on detecting any associated infections by routine cultures on admission for yersinia, salmonella, and shigella in the stools, for gonococci and *C. trachomatis* (samples from the urethra and cervix). In addition cultures from blood, throat, and other sites were taken when clinically indicated.

SEROLOGICAL METHODS

The following antibody assays were performed for the first two serum samples taken three to four weeks apart. Antibodies to *C. trachomatis* were assayed by the immunofluorescent antibody test; [14] to *Y. enterocolitica* serotypes 3 and 9 by a conventional agglutination method; antistreptolysin O (ASO), antistaphylolysin (ASta), teichoic acid antibody (TAA),[15] and streptococcal polysaccharide group A were assayed by a radioimmunoassay (RIA) method;[16] enterobacterial common antigen (ECA) by indirect haemagglutination;[17] salmonella O antigens 4, 12; 9, 12; and 6, 7 by Widal's test; viral antibodies to herpes simplex, varicella zoster, cytomegalovirus, adenovirus, influenza A and B, coronavirus, parainfluenza 1; 2; 3, mumps, respiratory syncytial virus, measles, rubella, polio, coxsackie virus B, rotavirus, *Mycoplasma pneumoniae*, and *Toxoplasma gondi* were assayed by a complement-fixation method; and HbsAg by a RIA method.

DIAGNOSTIC CRITERIA OF REACTIVE ARTHRITIS

The diagnostic criteria for reactive arthritis in this work were as follows: the general criteria were arthritis, HLA-B27 positivity, no clinical or microbiological evidence of purulent arthritis, exclusion of other known rheumatic disorders like gout, rheumatoid arthritis, and systemic lupus erythematosus. The additional diagnostic criteria for different triggering infections were as follows: *yersinia arthritis:* stool culture positive for yersinia and/or *Y. enterocolitica* antibodies (serotypes 3 or 9) positive with a titre of 1:320 or higher corresponding to the 99th percentile in a healthy Finnish adult population; *salmonella arthritis*: stool culture positive for salmonella and/or Widal's test positive (O antigens 4, 12; 9, 12; 6, 7) with a titre of 1:320 or higher (99th percentile); *shigella arthritis*: stool culture positive for shigella; *C. trachomatis arthritis*: *C. trachomatis* isolation from cervix or urethra positive and/or *C. trachomatis* antibodies positive with a titre of $\geq$ 1:256 (females) and $\geq$ 1:128 (males) corresponding to the 98th percentile; *gonococcal reactive arthritis*: *Neisseria gonorrhoeae* isolation from cervix or urethra positive and no clinical or microbiological evidence of purulent arthritis.

The high titre limits for positive results in other serological tests were as follows: ASO $\geq$ 500 Todd units (about 99th percentile),[18] teichoic acid antibodies $\geq$ 1:8 (99th percentile),[15] streptococcal group A polysaccharide antibodies $\geq$ 25 μg/ml (99th percentile),[16] and enterobacterial common antigen antibodies $\geq$ 1:4000 (about 98th percentile).[17] For positive viral antibody results the criteria were either a fourfold change in paired sera or a continuously high titre corresponding to the 98th–99th percentile levels in a healthy Finnish adult population.[18]

STATISTICAL METHODS

The χ^2 test with Yates's correction was the statistical method used.

Results

The triggering infection was determined in 35 (70%) of the 50 patients (Table 1) by the abovementioned criteria. In addition, two patients were not classified because they had serological evidence of two simultaneous infections. One of those two unclassified cases had high antibody titres against both *Y. enterocolitica* and *C. trachomatis*. The other had both a culturally and serologically proved *C. trachomatis* infection but also a high ASO titre (510 Todd units).

Y. enterocolitica and *C. trachomatis* were the most common triggering infections identified. Six patients had high ASO titres while all other microbiological and serological tests were normal, strongly suggesting group A streptococcus as the triggering agent. Two patients had high teichoic acid antibody titres, indicating a recent staphylococcal infection.

In most cases the diagnosis of the triggering infection was based on a high antibody titre already present in the first serum sample (Table 1). Stool cultures were negative in all 12 patients serologically identified as yersinia arthritis. Also in the majority of patients with *C. trachomatis* reactive arthritis the diagnosis was based on serology only. Only in one of the 11 chlamydia patients could the microbe be isolated from the cervix.

Data of a symptomatic infection up to three weeks before the onset of arthritis as based on the patients

Table 1 *Probable triggering infective agent in 50 HLA-B27 positive patients with reactive arthritis*

Probable triggering agent	*Number of patients*	*Identification of infective agent based on*		
		Positive serology		*Positive culture*
		*High titre**	*Fourfold change*	
Enterobacteriaceae				
Y. enterocolitica	12	12	3	0
Other†	4	3	1	1
C. trachomatis	11	10	0	1
β-Haemolytic streptococci‡	6	6	0	0
S. aureus§	2	2	0	0
Mixed‖	2	2	0	1
Unknown	13	0	0	0
Total	50	35	4	3

*Above the upper 98th–99th percentile level in a healthy Finnish adult population (for details see 'Methods').
†Includes two Widal-positive cases (probably salmonella), one culture-proved shigella gastroenteritis, and one ECA-positive case.
‡Includes six antistreptolysin O positive cases.
§Includes two teichoic acid antibody positive cases.
‖Includes one culture and serologically proven *C. trachomatis* case with simultaneously high ASO titre and one case with high yersinia-, anti-ECA, and chlamydia antibodies.

history are given in Table 2. Gastroenteritis or urogenital symptoms (dysuria or lower abdominal pain, or both) were good indicators for yersinia and chlamydia infections respectively, but several patients in all the aetiological groups had no clinically evident infection preceding the onset of arthritis symptoms.

The clinical picture in the different reactive arthritis groups was very similar (Table 3). The only significant difference between patients with yersinia and chlamydia reactive arthritis was the presence of fever in the former. Ten out of 12 yersinia patients had fever over 38°C at the onset of arthritis symptoms, but only one out of the 11 chlamydia patients had fever. This difference is statistically significant ($p<0.01$). The number in other groups was too small to allow definitive conclusions, but in general the clinical picture and laboratory parameters (Table 4) were very similar in all groups and independent of the triggering infection.

The anti-ECA titres in different patient groups are given in Fig. 1. As expected, the highest titres were seen in yersinia and other enterobacterial arthritis patients. No high anti-ECA titres were seen among the patients who were seropositive for chlamydia, streptococci, or staphylococci. One moderately high anti-ECA titre (1:2000) was seen in the unknown group; it could indicate a recent enterobacterial infection but did not quite meet the criteria for positive results (titre limit = 1:4000).

There were no diagnostic changes or very high titres in viral antibodies in any of the patients. All the patients were also HbsAg negative. The streptococcal group A polysaccharide levels and antistaphylolysin titres were also within the normal range in every case.

Discussion

The main difficulty in identifying the aetiology of the triggering infection in reactive arthritis is the time lag, as a rule from one to three weeks, between the infection and the onset of arthritis symptoms. Although this time lag is relatively short, it is often long enough to cause microbial cultures to become negative, and so in most cases the diagnosis of the triggering infection must be based on serological results only. The main difficulty in interpretation of

Table 2 *Correlation of a symptomatic preceding infection and the probable microbial aetiology in patients with reactive arthritis*

Probable triggering agent	*Number of patients*	*Preceding symptomatic infection**			
		Gastroenteritis	*Urogenital infection*	*Respiratory infection*	*No observed infection*
Enterobacteriaceae					
Y. enterocolitica	12	8			4
Other	4	1			3
C. trachomatis	11		8		3
β-Haemolytic streptococci	6			1	5
S. aureus	2			2	
Mixed	2		1		1
Unknown	13	3	2	2	6
Total	50	12	11	5	22

*Infection within three weeks before the onset of arthritis, symptoms as based on patients' history

Table 3 *Comparison of the clinical picture in different aetiological groups of reactive arthritis*

Probable triggering infective agent	*Number of patients*	*Fever ≥38°C*	*Joint involvement*				*Carditis*	*Eye symptoms‡*	*Classic Reiter's syndrome§*
			*Small joints**	*Large joints†*	*Back pain*	*X-ray changes in SI joints‖*			
Y. enterocolitica	12	10	6	12	4	1	0	3	1
Other enteric bacteria	4	3	3	4	2	0	0	1	0
C. trachomatis	11	1	6	11	8	1	1	0	0
β-Haemolytic streptococci	6	4	5	6	2	2	0	2	1
S. aureus	2	1	1	2	2	1	0	0	0
Mixed	2	0	2	2	0	0	0	2	1
Unknown	13	3	9	12	2	0	0	4	1
Total	50	22	32	49	20	5	1	12	4

*Includes metacarpophalangeal, proximal interphalangeal, or distal interphalangeal joints of hands and feet.
†Includes ankle, knee, hip, wrist, elbow, and shoulder joints.
‡Includes conjunctivitis and iritis.
§Includes the triad arthritis, conjunctivitis, and urethritis.
‖SI joints = sacroiliac joints.

Table 4 *Comparison of laboratory parameters in different aetiological groups of reactive arthritis*

Probable triggering infective agent	*ESR ≥20 mm/h*	*Anaemia**	*Leucocytosis†*	*Haematuria*	*Pyuria*	*Autoimmune tests positive*		*Raised serum immunoglobulins*		
						RF‡	*ANA§*	*IgM*	*IgG*	*IgA*
Y. enterocolitica	12/12‖	7/12	4/12	4/12	5/12	3/12	0/12	8/9	4/9	2/9
Other enterobacteria	4/4	1/4	1/4	1/4	2/4	0/4	0/4	2/3	0/3	0/3
C. trachomatis	8/11	2/11	3/11	1/11	5/11	2/11	0/11	3/11	2/11	3/11
β-Haemolytic streptococci	6/6	1/6	1/6	1/6	3/6	1/6	1/6	1/6	5/6	0/6
S. aureus	2/2	0/2	1/2	1/2	1/2	0/2	0/2	0/2	0/2	0/2
Mixed	1/2	0/2	0/2	0/2	1/2	0/2	0/2	1/2	0/2	0/2
Unknown	11/13	2/13	0/13	4/13	9/13	1/13	1/13	4/13	2/13	4/13
Total	44/50 (88%)	13/50 (26%)	10/50 (20%)	12/50 (24%)	26/50 (52%)	7/50 (14%)	2/50 (4%)	19/46 (41%)	13/46 (28%)	9/46 (20%)

*Haemoglobin ≤ 11 g/dl (females); ≤ 12 g/dl (males).
†Leucocytes ≥ 11 × 10^9/l.
‡Rheumatoid factor with latex test positive in titre ≥ 1:32.
§Antinuclear antibodies positive in titre = 1:100.
‖Number of positive patients/number of patients studied.
ESR = erythrocyte sedimentation rate.

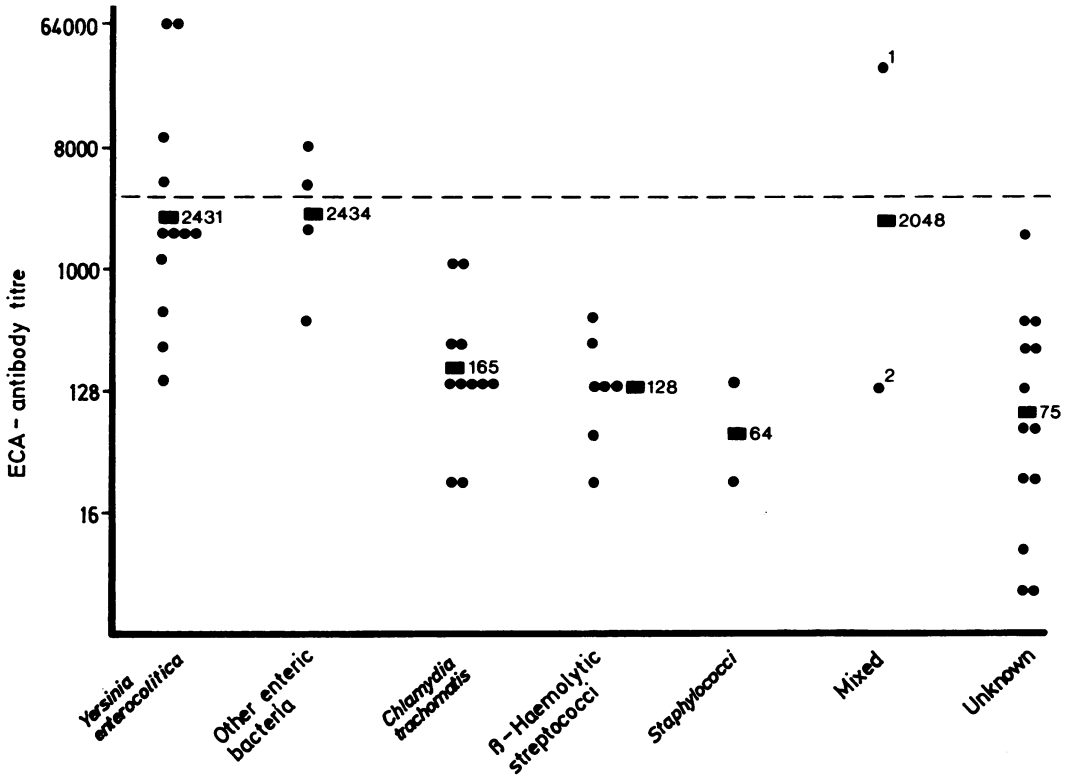

Fig. 1 *Anti-ECA titres in different patient groups. Heavy line represents geometric mean titre; dashed line denotes high titre limit for positive ECA test; 1=the patient had also high anti-yersinia and anti-chlamydia antibodies; 2=the patient had high anti-chlamydia and ASO antibody titre.*

the serological results derives from the same time lag, because of which the classically accepted diagnostic fourfold rise is not seen. Instead the highest titre is in most cases seen in the first serum sample, which of course was drawn after the onset of arthritis symptoms. High antibody values on the other hand must be assessed with care, based on a reference normal material. In this study we set a relatively high limit for a diagnostic high value (at the 98th–99th percentiles) in order to improve specificity by excluding possible antibody rises due to a polyclonal stimulation by another microbe. The lack of high values for a broad set of antiviral antibodies, and the concentration of positive findings to a few bacterial groups speaks for the specificity of the criteria set. On the other hand application of the strict limits probably decreased sensitivity and increased the unknown aetiology group. Nevertheless this group, in which no preceding infection could be diagnosed, was as small as 26%.

As a new serological test we applied determination of antibodies to ECA, an antigen common to all bacteria of the Enterobacteriaceae family. Thus gastroenteritis caused by yersinia, salmonella, and shigella (all well known triggers of reactive arthritis) would be expected to cause positive anti-ECA values. This was in fact found (Fig. 1), so that the mean anti-ECA in these patient groups was higher than any single value of patients with identified other, non-enterobacterial infections. However, not all patients with other evidence of an enterobacterial infection had high anti-ECA titres – even if the diagnostic limit had been lowered by one titre step one third of such patients would have been negative. Thus anti-ECA appears to have good specificity but rather low sensitivity in identifying the triggering infection of reactive arthritis.

Many different microbes and types of infection seem to be capable of triggering reactive arthritis in HLA-B27 positive patients, but the present series of 50 patients showed that the two definitely most common triggering infections at present in Finland are *Y. enterocolitica* gastroenteritis and *C. trachomatis* urogenital infections. Salmonella and shigella gastroenteritis are also known to be triggering

infections: we could identify three such patients. As separate, new entities we found patients who were seropositive only for streptolysin O (six patients), teichoic acid antibody (two patients), or anti-ECA (one patient). In only 13 patients (26%) we found no serological markers of a preceding infection.

Campylobacter is a recently recognised trigger of reactive arthritis,[6 7] and it might have been the most common agent in this unknown aetiology group. Unfortunately we had no means of detecting it in this study; a good serological assay for campylobacter infections can be expected to reduce further the unknown group. Campylobacter does not possess enterobacterial common antigen,[19] and therefore the moderately high anti-ECA antibodies associated with a history of gastroenteritis seen in two of the 'unknown' patients probably reflect some enterobacterial infection, e.g. salmonella of less common serogroups, or shigella. Anti-ECA could of course rise because of other enterobacterial infections, for example of *Escherichia coli* infections in the urinary tract.[19] Viral infections do not seem to have a role as triggering infections in HLA-B27 positive reactive arthritis, because no diagnostic changes or abnormally high titres were observed, though antibodies against 17 common viral agents were measured. This, of course, does not rule out the possibility of some viral infections, but it is far more probable that in the unknown aetiology group the triggering infection was bacterial.

The six ASO positive cases are of great interest. They fulfil the Jones diagnostic criteria for rheumatic fever,[20] but they differ from classical rheumatic fever in some important respects. The typical attack of rheumatic fever lasts only four to six weeks compared with three to four months for reactive arthritis. Lower back pain and eye symptoms (conjunctivitis, iritis) are rare in rheumatic fever, whereas eye symptoms were rather common in the present series. Carditis is probably more common in rheumatic fever – it was absent in all six ASO positive patients of the present series. The most important difference is, however, the HLA type. The classical rheumatic fever is not associated with the HLA type B27. We have previously studied patients with classical rheumatic fever[16] and observed high streptococcal group A polysaccharide antibody levels. In the present ASO, HLA-B27 positive cases the group A polysaccharide levels were in the normal range. This suggests a possible explanation for the different manifestation: the ASO positive triggering infection may have been caused by β-haemolytic streptococci other than group A – groups C and G also produce streptolysin O.[21] This difference may prove useful in the differential diagnosis of classical rheumatic fever and ASO, HLA-B27 positive reactive arthritis. However, it needs confirmation in a larger patient sample.

The genetic constitution (HLA type) of the patient is known to play a major role in determining the clinical picture of reactive arthritis.[11 13] However, the triggering infection appears to have some modifying effect. The most clear cut example of this is the absence of fever in chlamydia arthritis. This difference from yersinia arthritis was statistically highly significant but probably also true whenever the triggering infection was caused by other enteric bacteria or pyogenic cocci.

Knowledge of the triggering infection in reactive arthritis may be of help in the treatment or prevention of the disease. There are at the moment no good data for or against antibiotic treatment in reactive arthritis. Penicillin prophylaxis is of great help in the prevention of classical rheumatic fever, but whether it should be used also for the ASO positive, HLA-B27 positive reactive arthritis patients is not known. In the future, vaccination against the possible causes of the triggering infections may prevent reactive arthritis on the population level, but at the moment there are no vaccines against the two most common triggering infections, *Y. enterocolitica* and *C. trachomatis*. However, before vaccination could even be contemplated we must understand the pathogenesis of reactive arthritis better to avoid the possibility that vaccination itself might trigger the arthritis attack.

We thank Mrs Outi Vossi and Mrs Arja Ahokas for their skilful technical assistance. This study was supported in part by a grant from the Finnish Culture Foundation to Dr V Valtonen.

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