Reumatol Clin. 2018;14(1):36–39

Sociedad Española de Reumatología - Colegio Mexicano de Reumatología

Reumatología Clínica

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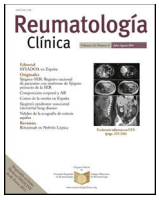

Brief report

Evolution over thirty years of the profile of inpatients with reactive arthritis in a tertiary rheumatology unit

Anne Brinster, Xavier Guillot, Clément Prati, Daniel Wendling*

Service de Rhumatologie, CHRU de Besançon and Université de Franche-Comté, Besançon, France

ARTICLE INFO

Article history:
Received 26 March 2016
Accepted 10 August 2016
Available online 4 September 2016

Keywords:
Reactive arthritis
Spondyloarthritis
Epidemiology
Treatment
Outcome

ABSTRACT

Reactive arthritis (ReA) is sterile arthritis occurring after extra articular bacterial infection. The aim of this study was to analyze, over 30 years, clinical, biological and imaging characteristics as well as therapeutic management of new cases of ReA, comparing two periods.

Methods: retrospective monocentric study, data of all the patients followed in our unit between January 1st 1984 and April 2014 with the diagnosis or ReA were analyzed (clinical and biological features, management and outcome), and compared between two periods: from January 1984 to December 1993, and from January 2004 to December 2013.

Results: Sixty two patients fulfilling international diagnosis criteria were analyzed. There was no significant difference between the two periods in number of new cases, clinical presentation, biological data or outcome. Changes in therapeutic management were obvious with occurrence of anti TNF in the recent period.

Conclusion: Reactive arthritis is still a current rheumatologic problem in a developed country, with a need of early and tailored rheumatologic management.

Evolución durante 30 años del perfil de pacientes hospitalizados con artritis reactiva en una unidad de reumatología de tercer nivel

Palabras clave:
Artritis reactiva
Espondiloartritis
Epidemiología
Tratamiento
Resultado

RESUMEN

Las artritis reactivas (ARe) son artritis estériles que se manifiestan después de una infección bacteriana extraarticular. El objetivo de este estudio es analizar, durante 30 años, las características clínicas, biológicas e imagenológicas, así como la gestión del tratamiento de la ARe, mediante la comparación de 2 periodos.

Métodos: Estudio retrospectivo monocéntrico. Se analizaron los datos de todos los pacientes diagnosticados con ARe en nuestra unidad entre el 1 de enero de 1984 y abril de 2014 (rasgos clínicos y biológicos, gestión y resultados) y se compararon con 2 periodos: de enero de 1984 a diciembre de 1993, y de enero de 2004 a diciembre de 2013.

Resultados: Se analizaron los datos de 62 pacientes que cumplieron los criterios de diagnóstico internacionales. No existió una diferencia significativa entre los 2 periodos en la cantidad de casos, presentación clínica, datos biológicos o resultados. Los cambios de la gestión del tratamiento fueron evidentes, con la aparición de anti-TNF en el periodo reciente.

Conclusión: La artritis reactiva continúa siendo un problema reumatológico actual en los países desarrollados, con una necesidad de tratamiento reumatológico temprano y personalizado.

* Corresponding author.
E-mail address: dwendling@chu-besancon.fr (D. Wendling).

Reactive arthritis (ReA) is defined as arthritis developing 2–4 weeks after extra articular infection, without evidence of microorganism in the joint using classical culture tools.[1,2] The triggering infection is mainly located in gut or genito urinary mucosa. The classical clinical presentation is an acute oligo arthritis, mainly located at the lower limbs, with possibility of axial (sacro iliac and spine) involvement and enthesitis, as well as extra articular features (ophthalmologic or dermatologic symptoms). ReA is considered part of spondyloarthritis spectrum, sharing with this entity common clinical and imaging features, as well as frequent association with HLA-B27 haplotype.[3,4] Outcome is variable, with possibility of resolution after several months, or relapses or chronic evolution, leading sometimes, after years, to ankylosing spondylitis.

The aim of this study was to analyze, over 30 years, in new cases of ReA the clinical, biological and imaging characteristics, as well as management modalities, comparing two periods.

Patients and methods

This is a descriptive, monocentric retrospective study of patients hospitalized in the Rheumatology department of the Centre Hospitalier Régional et Universitaire in Besançon, France, between January 1st 1984 and april 2014 with ReA as principal diagnosis, according to ICD codes M02 and M03. The charts were reviewed by experienced rheumatologists (AB, CP, DW) and patients were included if they fulfilled international classification criteria.[2] The following data were recorded: demographic characteristics, HLA-B27 status, initial infection (location and bacteriological species) and its diagnosis method, as well as the potential antimicrobial treatment. Clinical features of ReA were noted: delay between infection and rheumatologic symptoms onset, general symptoms (fever), tender and swollen joint counts, presence of enthesitis or dactylitis, axial symptoms, and extra articular symptoms (conjunctivitis, uveitis, balanitis). The rheumatic treatments and their introduction delay were collected, as well as the outcome. For this purpose, we studied and compared charts of patients with ReA over two periods, from January 1984 to December 1993, and from January 2004 to December 2013.

Results were expressed as numbers for the microbiological findings, and means or percentage for clinic-biological data. χ^2 test were used for comparisons of percentages, with Yates and Fisher corrections if needed, and Mann–Whitney if t test were not applicable. Significance threshold was p less than 0.05.

Results

One hundred and twenty charts were analyzed, and 62 were finally included, the causes of exclusion were wrong diagnosis and absence of classification criteria fulfilment. They were 52 men (83.9%) and 10 women (16.1%) with a mean age of 34 years (12–69). Six patients (10%) had a familial history of inflammatory rheumatic disease, four of them had a familial background of spondyloarthritis. At admission, 20% of the patients were febrile, and 82% had elevated biologic markers of inflammation (mean CRP 94 mg/l, leukocytes (WBC) 10.2 G/l). A complete urethro-oculo-synovial syndrome was noted in 19.4%. The mean number of painful joints was 3, and of swollen joints 2.1; two patients had no synovitis, but in one case we noticed axial symptoms with buttock pain and a dactylitis. The most frequently involved joints were the knee, then ankle, wrist and tarsal joints; dactylitis was present in 19.4% of the cases. Inflammatory back pain was mentioned in 22.3% of the cases, and enthesopathy in 24.2%, mainly talalgia. Among extra rheumatic involvement, conjunctivitis was the most frequent (27.4%); three cases of palmar and/or plantar pustulosis and three cases of balanitis were observed. HLA-B27 typing was positive in 36 out of 56 assessments (64.3%).

Table 1
Distribution of infectious agents.

Infectious agent	Number of patients positive	Serology	PCR	Culture
Chlamydia trachomatis	18	14	2	
Ureaplasma urealyticum	5	0	5	
N. gonorrhoea	4	3	1	
Mycoplasma pneumoniae	2	2	0	
Chlamydia + Yersina	1	1		
Chlamydia + Strepto B	1		1	
Chlamydia + N. gonorrhoea	1	X	X	
Salmonella	1			1
Neisseria meningitidis	1			1
Anguillulosis	1	1		
Streptococcus B	1		1	
Yersina	1	1		
S. Aureus + Strepto B	1		1	
Not found	22			

PCR: polymerase chain reaction.

Urethritis was described in 43.6% and dysenteric syndrome in 21% of the cases. Eight cases exhibited no infectious symptoms, and in 7 of them, evidence of an infection was brought by systematic research. Rheumatologic symptoms appeared with a mean of 14.7 days after the supposed infection. Evidence of infection was found in 63.3%, with serological proof in 37%, PCR on urethral sampling in 14% and vaginal in 2%, blood and stool cultures in 2% of the 62 cases each. *Chlamydiae trachomatis* was the most frequent infectious agent (37% of the cases with evidence of infection), found in 83.3% by serology, 11% by PCR (uretral or vaginal), and 5.6% by both methods; in three cases it was associated with another infection (*streptococcus*, *Yersinia*, *gonococcus*). The following most frequent species were *Ureaplasma urealyticum* and *Neisseriae gonorrhoeae* (Table 1). In 35 cases, an antibiotic treatment for the inaugural infection was mentioned.

Non steroidal anti inflammatory drugs (NSAIDs) were used in 91.8% of cases. The absence of use was due to contra indications or intolerance. Disease modifying anti rheumatic drugs (DMARDs) were introduced in 51.8% of patients with a median delay of 60 days from the first rheumatic symptoms, with salazosulfapyridin as the first choice. Use of TNF blockers was recorded in 15 patients (24.2%), mean age 35 years, with a median delay of 116 days.

The outcome was variable, and longstanding follow-up was available in 42 patients: with a mean follow-up duration of 34 months, 52% are in remission, under or without treatment, 44% developed spondyloarthritis, and 4% psoriatic arthritis,.

The comparison of the two cohorts did not reveal any significant change in the frequency of ReA in hospitalized patients or in the profile of these patients (Tables 2 and 3) (age, sex, type of infection, rheumatologic presentation or outcome). In the most recent period, the use of Azithromycin for treatment of Chlamydia, and of anti TNF agents were more frequent.

Discussion

Reactive arthritis may have two backgrounds: epidemic, with classical description during world war 1st,[5] and sporadic. It corresponds to arthritis related to a preceding infection outside the joint, mainly in the gut[6] or the genito urinary tract, with some classical species,[7] and other less frequent (e.g. *Clostridium*[8] or *N. gonorrhoea*).[7] The estimated annual incidence varies among studies and countries between 0.6 and 30/1,000,000 (4). Due to improvement in collective hygienic conditions, one may expect a reduction in incidence of ReA in developed countries. It has been recently shown a decline in ReA diagnoses despite an increase

Table 2
"Global" comparison of the 2 cohorts.

	1984–1993	2004–2013	*p*
Number of patients included	15	31	0.4
Number of patients hospitalized	7438	11 823	
Men	13	28	0.6
Median age at diagnosis	37	30	0.9
HLA B27+ (%)	91	63	01
Delay between infection/articular symptoms (days) median	5.5	9	0.6
mean	14.2	14	
Patients with fever (%)	20	19	1
Leucocytes (giga/l)	9.8	10.6	0.4
CRP (mean) (mg/l)	87.4	90.1	0.9
Evidence of infectious agent (%)	53	61	0.2
Antibiotic treatment (%)	77	93	0.3
Treatement by azithromycin (%)	0	47	0.006
TJC/SJC	2.8/1.8	3.2/2	ns
Dactylitis (%)	13	29	0.3
Enthésitis (%)	40	26	0.5
Extra articular features (%)	47	35	0.4
Axial symptoms (%)	33	29	1
DMARDs use (%)	36	62	0.1
Median delay of DMARD introduction (days)	210	50.5	ns
Biologic agents use (%)	0	45	0.005
Remission at last follow-up (%)	57	47	0.6

(ns = non significant) TJC: tender joint count; SJC: swollen joint count, DMARDs: disease modifying anti rheumatic drugs.

Table 3
Distribution of infective agents found in cases of reactive arthritis between the two periods.

Infectious agent (%)	1984–1993 (*N* = 15)	2004–2013 (*N* = 31)	*p*
Chlamydia	33	31	1
N. gonorrhoea	7	7	1
Mycoplasma	0	7	0.54
Ureaplasma	0	7	0.54
Salmonella	0	3	1
Anguillulosis	0	3	1
Yersinia	7	3	1
Not found	53	61	ns

in chlamydia diagnoses over the 1992–2012 period in Sidney, Australia.[9] Our results do not share this conclusion, in fact, the incidence of new cases of ReA in our department seems similar between the two periods of analysis (Table 2), *Chlamydia* being the most frequent incriminated (Table 1).

The microbiological profile of potential triggers is tributary of the detection method. Direct evidence of infection is difficult to obtain, since the micro organism is no more present at the site of infection when arthritis occurs,[7] and indirect assessments, mainly serologic tests, have limitations.[10] The profile of microbiological species is not different between the recent period and 30 years ago in our series, with a similar proportion of bacteriological evidence missing despite use of new techniques in the recent period (e.g. polymerase chain reaction).

The clinical presentation of rheumatologic features and extra articular manifestations did not differ significantly between the two periods.

Some changes were obvious in the therapeutic management. The type of antibiotics used for the treatment of the initial infection changed over the years, due to availability of new treatments, whereas, efficacy of antibiotics upon rheumatologic symptoms is still not demonstrated.[11] The use of conventional synthetic DMARDs is similar over the two periods, but the use of anti TNF agents appear in the recent period; efficacy and safety of TNF blockers were observed in case reports[12] and observational series[13] in the recent years.

The outcome is more difficult to analyze, since one third of the patients were lost of follow-up after six months in the whole population. For patients with follow-up, half of them was considered in remission, with or without treatment, and the remaining developed chronic spondyloarthritis, illustrating the several phenotypes of the disease.[14] Again, no significant changes were obvious in outcome between the two periods of observation. A recent paper analyzed the outcome of 21 cases of epidemic outbreak of ReA after waterbone gastro enteritis[15]: after one year, one third of the patients demonstrated a chronic evolution, defined as a duration of arthritis over 6 months.[4]

Our study has some limitations. The retrospective analysis, and some missing data, particularly in follow up, dim the conclusions. The absence of universal classification criteria, associated with the difficulty of diagnosis in cases without the evidence of infection represent another limitation. Referral biases arise for this kind of study, and the analysis performed only on inpatients in one department of the hospital. Due to the acute presentation, patients were referred via the general practitioner or the emergency room, without major change over the two periods (data not shown). Nevertheless, the large period of monocentric observation and the number of patients provide some interest for this analysis.

Our study confirms that ReA is still present in a tertiary rheumatology unit in a developed country, without major changes over 30 years in clinical presentation and microbiologic context. ReA keeps a potential evolution towards chronicity that justifies an early rheumatologic management and follow-up with tailored treatment.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors declare no conflict of interest concerning this manuscript.

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