SPECIAL ARTICLE

REITER'S SYNDROME

Evaluation of Preliminary Criteria for Definite Disease

ROBERT F. WILLKENS, FRANK C. ARNETT, THOMAS BITTER, ANDREI CALIN, LLOYD FISHER, DENYS K. FORD, ARMIN E. GOOD, and ALFONSE T. MASI

A retrospective evaluation of 83 patients with Reiter's syndrome (RS) and 166 comparison arthritis patients was conducted in order to assess the preliminary criteria for definite RS. Data analysis was based on the statement that Reiter's syndrome consists of an episode of peripheral arthritis of more than 1 month duration occurring in association with urethritis and/or cervicitis. During the initial episode of RS, 70 of the 83 RS patients satisfied the criteria, yielding a sensitivity of 84.3%.

The extensive overlap of clinical manifestations of the various seronegative spondylarthropathy syndromes makes it difficult to define a specific disease within that group of disorders (1). The discovery that HLA–B27 is found in a high proportion of such patients has helped to focus on the interrelationships of these disorders (2).

This report describes an effort to define "definite" Reiter's syndrome by a retrospective evaluation of typical cases submitted from seven university-based arthritis centers. The investigation has been underway for a number of years, and selection of cases preceded knowledge of histocompatibility types. In a sense, the proposed criteria provide a clinical definition of a patient group which may subsequently be recognized by other markers.

From the University of Washington, Seattle, WA; Johns Hopkins University, Baltimore, MD; University of Lausanne, Lausanne, Switzerland; Stanford University, Stanford, CA; University of British Columbia, Vancouver, BC, Canada; University of Michigan, Ann Arbor, MI; Peoria School of Medicine, Peoria, IL.

Address reprint requests to Robert F. Willkens, MD, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104.

Submitted for publication December 22, 1980; accepted January 9, 1981.

STUDY DESIGN

Participating centers contributed specific protocol evaluations of patients in five disease categories: Reiter's syndrome (RS), ankylosing spondylitis (AS), seronegative rheumatoid arthritis (SNRA), psoriatic arthritis (PsA), and gonococcal arthritis (GcA). The patients selected were "typical" in the investigator's experience. Sixty-six discrete variables (a selection is given in Table 1) believed by the investigators to have value in the discrimination and classification of RS were analyzed univariately for their presence or absence in Reiter's syndrome patients by the Chi-square test and visual inspection. Variables that seemed especially useful were examined in four-way or less contingency tables to examine their power of classification. Multiple discriminant function analysis was also used to discriminate between the groups, and between subjects with Reiter's syndrome versus all other patients. Previously proposed provisional criteria were modified on the basis of these results.*

Urethritis is defined as a genitourinary inflammation with evidence of slight, moderate, or profuse mucopurulent or seropurulent discharge. If the discharge is scanty, it may be demonstrable only in the morning after urination. Dysuria may be found, often without discharge, and is indicative of recent cystitis or urethritis. Rarely and more problematical is the presence of only recent asymptomatic pyuria. If Reiter's syndrome is accompanied by gonococcal urethritis, the urethral discharge may persist after the administration of an adequate dose of penicillin sufficient to eradicate the gonococci.

* A previous subcommittee for the classification of Reiter's syndrome of the American Rheumatism Association (ARA) Diagnostic and Therapeutic Criteria Committee had proposed that a diagnosis be established on the basis of the occurrence of certain clinical manifestations. The designations of these manifestations were more clearly delineated by categorizing them as major and minor. Using these criteria, a diagnosis of definite Reiter's syndrome could be made if three major manifestations occurred. An individual could be considered to have probable or incomplete RS if arthritis occurred within 3 to 6 weeks after urethritis, with or without the presence of mucosal lesions. Alternately, probable disease was possible when one major and three minor criteria occurred within a 6-week period.

Table 1. Percentage of Reiter's syndrome case and comparison patients with positive findings during the initial attack*

Sign or symptom	% RS (n = 83)	% AS (n = 53)	% SNRA (n = 33)	% PsA (n = 53)	% GcA (n = 27)
Arthritis (including spinal)	99	100	100	100	100
Tendinitis	25	12	7	6	23
Heel pain	40	12	0	4	8
Back pain	49	87	0	28	4
Polyarticular	81	29	68	84	54
Monarticular	14	8	30	15	30
Sausage digits	17	6	0	52	0
Urethritis, males and females	85	4	0	0	38
Cervicitis (number of females)	71(7)	0(6)	0(18)	0(13)	33(18)
Conjunctivitis, any	57	20	0	4	0
Bilateral	44	8	–	4	–
Mucous membrane lesions	31	0	0	2	12
Skin lesions	49	2	0	96	54
Multiple locations	21	2	–	90	54
Nail changes	9	0	–	67	0
Balanitis	39	0	–	2	0
Diarrhea	14	4	0	0	4
CNS involvement†	1	2	0	0	0
Fever	37	2	6	4	50
Weight loss	38	4	9	12	0
Acute attack	77	25	32	19	100
Duration of initial attack					
1 week or less	0	2	4	2	42
1 week–1 month	1	7	4	0	46
Longer than 1 month	99	91	92	98	12
Positive family history	13	33	29	30	0
HLA-B27 positive (number typed)	86(77)	97(37)	33(6)	47(19)	0(1)
Joint x-ray abnormalities					
Peripheral (number cases)	11(45)	23(22)	64(14)	47(19)	46(11)
Sacroiliac (number cases)	22(37)	80(15)	11(9)	13(16)	0(4)

* RS = Reiter's syndrome; AS = ankylosing spondylitis; SNRA = seronegative definite rheumatoid arthritis; PsA = psoriatic arthritis; GcA = gonococcal arthritis.
† CNS = central nervous system.

Table 2. Percentage of patients with tenderness or swelling of joints during the initial episode and last examination*

Joints involved	% RS (n = 74/72)†	% AS (n = 27/49)	% SNRA (n = 29/23)	% PsA (n = 31/51)	% GcA (n = 24/—)
Jaw	1/1	0/2	0/6	6/0	0/—
Neck	7/3	4/2	0/3	0/4	0/—
Arms, shoulders, wrists	28/12	22/29	59/79	51/61	67/—
Hands	23/14	4/4	55/76	65/67	25/—
Sacroilic	14/8	37/53	0/0	7/8	0/—
Hips	7/7	26/14	7/15	3/6	0/—
Knees or ankles	61/28	22/14	72/63	52/45	75/—
Heels	26/13	0/8	14/30	8/10	13/—
Feet	16/15	0/2	21/27	45/45	8/—
Asymmetric involvement for tenderness and/or swelling					
Heels	32/10	0/8	5/14	6/7	2/—
Feet	20/15	0/1	1/5	21/26	4/—

* RS = Reiter's syndrome; AS = ankylosing spondylitis; SNRA = seronegative definitive arthritis; PsA = psoriatic arthritis; GcA = gonococcal arthritis.
† % during initial episode/% during final examination.

Table 3. Percent sensitivity and specificity of proposed criteria for typical Reiter's syndrome

	Percent	Number correctly classified/ number tested
Sensitivity		
At initial episode	84.3	70/83
Including subsequent attacks	97.6	81/83
Specificity against*		
All other cases	98.2	163/166
Ankylosing spondylitis	96.2	51/53
Seronegative definite rheumatoid arthritis	100.0	33/33
Psoriatic arthritis	100.0	53/53
Gonococcal arthritis	96.3	26/27

* Initial episode.

The mucocutaneous lesions of Reiter's syndrome may be keratodermia blennorrhagicum, balanitis circinata sicca, or oral mucosal lesions. Keratodermia blennorrhagicum usually begins on the palms and soles as pustules. Gradually they become covered with thick, horny crusts. Neighboring lesions may become confluent, and similar lesions can develop on all cutaneous areas. Clinically, cutaneous lesions are difficult to differentiate from pustular psoriasis.

RESULTS

Two hundred forty-nine protocols on case and comparison patients were submitted from seven centers* and analyzed for 66 variables. A selection of these variables is shown in Table 1; percentage may be based upon data which were not complete in all cases. Disease manifestations of RS such as myocarditis were evaluated, although no patients in any of the disease categories studied were found to have this variable.

Virtually all 249 patients had peripheral or spinal arthritis as a component of their initial attack. Polyarticular presentation, i.e. four or more joints involved, greatly exceeded monarticular onset.

Diffuse swelling of a toe, the classic "sausage digit" (or dactylitis), occurred in 17% of RS patients, but the frequency was much greater (52%) in patients with psoriatic arthritis. An acute attack of disease had occurred in 75% of patients with RS, all of those with GcA, and 32% of those with SNRA.

Articular tenderness and/or swelling was assessed to determine the regions of the body involved and symmetry (Table 2). Involvement of the knees or ankles occurred in 61% of the RS patients in their initial attack, and heels were swollen or tender in 26%. Heel involvement was asymmetric in 32% of RS patients in whom it occurred. Asymmetric involvement of joints was not a distinguishing characteristic of the arthritis of RS in comparison to the other diseases studied.

The data analysis was simplified by the proposal that *Reiter's syndrome consists of an episode of peripheral arthritis of more than 1 month duration occurring in association with urethritis and/or cervicitis.* Other more complex combinations were considered less helpful.

Table 3 indicates the sensitivity and specificity of the proposed criteria. Sensitivity is the percentage of accepted RS cases that satisfy criteria, and specificity is the percentage of comparison patients who do *not* satisfy criteria. During the initial episode, 70 of the 83 Reiter's patients satisfied criteria yielding a sensitivity of 84.3%. Of the 13 RS patients incorrectly classified, 1

Table 4. Percent sensitivity and specificity of various criteria for typical Reiter's syndrome*

Method of classification	Sensitivity†	Specificity†
1. Episode of arthritis of more than 1 month with urethritis and/or cervicitis	84.3% (70/83)	98.2% (163/166)
2. Episode of arthritis of more than 1 month and *either* urethritis or cervicitis, *or* bilateral conjunctivitis	85.5% (71/83)	96.4% (160/166)
3. Episode of arthritis, conjunctivitis, and urethritis	50.6% (42/83)	98.8% (164/166)
4. Episode of arthritis of more than 1 month, conjunctivitis, and urethritis	48.2% (40/83)	98.8% (164/166)

* Initial episode.
† Numbers in parentheses indicate number of patients correctly classified/number tested.

Table 5. Percentages of specified signs and symptoms present during the initial episode of Reiter's syndrome among patients who did and did not satisfy proposed criteria

Signs and symptoms	% RS patients satisfying criteria (n = 70)	% RS patients not satisfying criteria (n = 13)
Bilateral conjunctivitis	52	15
Unilateral conjunctivitis	6	0
Balanitis	46	8
Mucous membrane	34	0
Heel pain	44	25
Fever	41	10
Weight loss	40	18

* University of Washington, Stanford University, Johns Hopkins University, University of British Columbia, University of Michigan, University of Tennessee, Centre for the Health Sciences, University of Lausanne in Switzerland, New York University.

Table 6. Secondary signs and symptoms associated with Reiter's syndrome and comparison diseases*

Number present	Reiter's syndrome: Criteria positive	Reiter's syndrome: Criteria negative	Ankylosing spondylitis	Seronegative rheumatoid arthritis	Psoriatic arthritis	Gonococcal arthritis
6	5	0	0	0	0	0
5	4	0	0	0	1	0
4	10	0	0	0	0	0
3	11	1	1	0	0	0
2	10	1	0	2	3	4
1	14	4	10	1	3	7
0	9	7	42	30	46	15

* Signs and symptoms are: bilateral eye involvement, fever, weight loss, heel pain, balanitis, and mucous membrane lesions.

male had a duration of initial episode of 2 to 4 weeks. The other 11 males did not have urethritis. In 11 of the 13 individuals, a subsequent attack of arthritis and urethritis occurred. The duration of the subsequent attack or attacks was not assessed, but if one assumes an episode enduring more than 1 month, 81 of 83 Reiter's patients would be correctly classified during the course of followup.

Alternative criteria were considered which included the classic definition of RS as the triad of arthritis, urethritis, and conjunctivitis, with and without defining time limits. Comparison of the sensitivity and specificity of alternative criteria is shown in Table 4.

Three comparison patients were misclassified using the proposed criteria. Two of them were entered as having ankylosing spondylitis; both of these patients had unilateral conjunctivitis and heel pain, as well as satisfying the criteria for RS. The third patient with GcA satisfied the criteria, as well as displaying heel pain and fever. The specificity of the criteria was 98.2% during the initial episode.

DISCUSSION

The development of criteria in the rheumatic diseases has followed an evolution in concept and application. The criteria for rheumatoid arthritis, for example, were developed and proposed by a small group of physicians on the basis of their clinical experience (3). Limited testing of those criteria was undertaken prior to their suggested acceptance. This contrasts with the method used to arrive at the 14 criteria now proposed for the classification of systemic lupus erythematosus (SLE) (4). The criteria for SLE are based on a critical analysis of 245 patients with unequivocal SLE, 204 with probable SLE, and 451 patients with rheumatoid arthritis and other disorders. Fifty-two rheumatologists at 59 hospitals and clinics were involved in contributing retrospective protocol data to that study.

A more critical analysis is one in which criteria are derived from predefined prospectively gathered data, and the patients are followed for a sufficient period to confirm the study diagnosis and document the natural history or prognosis of the disease, e.g., the recent study of classification criteria for systemic sclerosis (scleroderma) (5).

Inherent difficulties exist in accomplishing such a study in RS and the control diseases from which it must be differentiated. For example, the disease may be transient, long-term followup is difficult, symptoms and signs may be temporally spaced, and radiographic changes are usually not apparent until later in the disease course (6). For these reasons, we chose to evaluate case records of "typical" patients in an attempt to develop initial criteria for definite RS.

To derive the criteria, detailed search for disease

Table 7. Proportion of Reiter's patients having selected manifestations according to B27 positivity or negativity

Selected manifestations	Positive (n = 63)*	Negative (n = 11)†	*P* value‡
Urethritis	51/62	10/11	NS
Conjunctivitis	34/63	7/11	NS
Mucous membrane	14/54	3/10	NS
Heel pain	25/59	5/11	NS
Polyarticular arthritis	54/63	7/11	NS
Sacroiliac involvement, x-ray (initial episode)	6/29	0/4	NS§
Last exam	15/46	2/9	NS
Skin lesions	31/59	2/10	0.04§
Weight loss	22/55	2/9	NS
Fever	18/55	4/9	NS

* Number B27 positive/number with manifestations.
† Number B27 negative/number with manifestations.
‡ Chi-square analysis with continuity correction. NS = not significant.
§ Two-sided Fischer's exact test.

patterns utilized both clinical intuition and computer assistance, e.g. discriminant function analysis programs. None of the more complex definitions was superior in classification ability to the one proposed. This being the case, the simplest classification criteria were selected. These criteria do not negate the importance in diagnosis of a variety of signs and symptoms which commonly occur in Reiter's syndrome. The other manifestations usually occur at the same time as the appearance of urethritis and/or cervicitis.

Table 5 indicates the percentage of selected signs and symptoms which occur in RS. Patients meeting the proposed criteria had higher percentages of these disease manifestations.

Table 6 makes the same point in a different fashion. The number of patients with different combinations of the six specified signs and symptoms were determined for each disease category. For example, 10 AS patients manifested only one of the six features. The RS patients satisfying the criteria had significantly more manifestations (an average of 2.4) than those not meeting the criteria (an average of 0.7). Secondly, 40% of the RS patients had three or more clinical findings, while only 1.8% of the comparison patients had three or more. Clearly these manifestations predominate in RS, especially in those patients who satisfy the proposed criteria.

Roentgenographic findings were part of an earlier set of proposed criteria, but they were found to be of no help in the diagnosis of an acute episode of RS. Data on sacroiliac joint involvement subsequent to the initial episode were reviewed. Of 13 RS patients presenting with fever, 44.3% later developed sacroiliitis versus 24.3% of 33 patients who did not have fever initially. These data are not statistically significant, but fever and other systemic manifestations merit critical attention in long-term studies of patients with RS (6).

The occurrence of selected clinical manifestations was analyzed in relation to the presence or absence of HLA–B27 positivity (Table 7). Little difference was found, although B27 positivity was associated with more frequent skin lesions ($P = 0.04$) and possibly with more frequent weight loss ($P = 0.09$). With the small number of HLA–B27 negative cases studied, it is difficult to demonstrate such differences.

Twelve of the 13 patients not fulfilling the criteria had arthritis. Five of these individuals had secondary manifestations, and all but 1 was HLA–B27 positive. One patient with a disease episode of less than 1 month which was characterized by urethritis, arthritis, and conjunctivitis was B27 negative. Although asymmetric lower extremity involvement occurred frequently in RS, Table 2 shows similar distribution in SNRA.

This retrospective evaluation of 83 typical RS patients and 166 comparison arthritis patients has provided a characterization of the initial attack of what might be considered definite RS. Such clinical syndromes can be distinguished with increasing confidence, depending upon the extent of associated manifestations other than arthritis of longer than 1 month duration and urethritis or cervicitis.

This report has not thoroughly addressed the issue of RS patients who do not fulfill the primary criteria nor the issue of other forms of reactive arthritis which mimic RS. These important questions will require more extensive prospective and immunogenetic correlation.

The problem of recognizing the patient with long established RS who may now be diagnosed as having AS or PsA (7) or the individual with reactive arthropathy alone is not satisfactorily addressed by this study. The categories of incomplete Reiter's syndrome (6), reactive arthritis (8), ankylosing spondylitis, psoriatic arthritis, and seronegative rheumatoid arthritis probably represent heterogenous patient groupings. These classifications are being examined by other groups of investigators (9,10).

ACKNOWLEDGMENTS

The authors wish to express their appreciation to Drs. Currier McEwen and Arnold Soren of New York University for use of their case histories, and to Jan Lamers and Jane Lucas for their help in data processing.

REFERENCES

1. Wright V: Seronegative polyarthritis: a unified concept. Arthritis Rheum 21:619–623, 1978
2. Brewerton DA: HLA B27 and the inheritance of susceptibility to rheumatic disease. Arthritis Rheum 19:656–668, 1976
3. Ropes MW, Bennett GA, Cobb S, et al: Diagnostic criteria for rheumatoid arthritis. Bull Rheum Dis 9:175–176, 1958
4. Cohen AS, Reynolds WE, Franklin EC, et al: Preliminary criteria for the classification of systemic lupus erythematosus. Bull Rheum Dis 21:643–648, 1971
5. Masi AT, Rodnan GP, Medsger TA, Altman RD, D'Angelo WA, Fries JF, LeRoy EC, Kirsner AB, MacKenzie AH, McShane DJ, Myers AR, Sharp GC: Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 23:581–590, 1980
6. Calin A: Reiter's syndrome, Textbook of Rheumatology. Edited by WN Kelley, ED Harris Jr, S Ruddy, CB

Sledge. Philadelphia, WB Saunders Company, 1980, pp 1033–1046
7. Khan MY, Hall WH: Progression of Reiter's syndrome to psoriatic arthritis. Arch Intern Med 116:911–996, 1965
8. Polyarthritis and *Yersinia entercolitica* infection. Br Med J 2:404–405, 1975
9. Masi AT, Maldonado-Cocco JA, Kaplan SB, et al: Prospective study of the early course of rheumatoid arthritis in young adults. Semin Arthritis Rheum 5:299–326, 1976
10. Schaller JG: The diversity of JRA: a look at the subgroups of chronic childhood arthritis. Arthritis Rheum 20:52–63, 1977

THE OGRYZLO INTERNATIONAL FELLOWSHIP

Dr. Gianfranco Ferraccioli of the University of Parma in Italy was the successful candidate for the second Ogryzlo International Fellowship for training in rheumatology. Commencing in July 1981, he will study rheumatology at The Royal Victoria Hospital Division of the McGill University Rheumatic Disease Unit, under the direction of Dr. C.K. Osterland.

The third Ogryzlo Fellowship will be for training in rheumatology at a Canadian Rheumatic Disease Unit for the 12 months commencing July 1, 1982. Applications must be submitted to The Arthritis Society, 920 Yonge St., Ste. 420, Toronto, Ont. Canada M4W 3J7 by October 15, 1981. Application forms and regulations may be obtained from the Society. Canadian citizens and landed immigrants to Canada are not eligible.

The Ogryzlo Fellowship carries a stipend of $20,000 U.S. per annum. This Fellowship is a gift by members of the Canadian Rheumatism Association in memory of their late colleague, Dr. Metro A. Ogryzlo.