Lack of Association with Spondyloarthritis and HLA-B27 in Italian Patients with Whipple's Disease

IGNAZIO OLIVIERI, GIOVANNI BRANDI, ANGELA PADULA, MICHELE DI STEFANO, WILMA MANTOVANI, CARLO CALABRESE, GIOCONDA SACCOCCIO, GIULIO DI FEBO, GINO ROBERTO CORAZZA, MARIO MIGLIOLI, and GUIDO BIASCO

ABSTRACT. ***Objective***. To examine consecutive patients with Whipple's disease (WD) for the full clinical spectrum of spondyloarthritis.

Methods. Nine consecutive patients, 8 men, 1 woman, with WD were clinically evaluated and examined for clinical and radiological manifestations of spondyloarthritis by 2 rheumatologists with special interest in spondyloarthritis. The mean age of the patients at the time of study and at the time of their initial diagnosis of WD by duodenal biopsy was 62.4 years (range 42–71) and 54.4 years (range 40–62), respectively. Each patient had an anteroposterior radiographic view of the pelvis and also had HLA typing for class I and II alleles. Pelvis radiographs were read blindly for evidence of sacroiliitis.

Results. All but one patient had rheumatologic manifestations related to WD. The mean interval between the onset of these symptoms and the diagnosis of WD was 6.1 years (range 1–15). One had recurrent polyarthritis, 1 recurrent oligoarthritis, 3 recurrent monoarthritis, 2 recurrent synovitis with pitting edema of the dorsum of hands and/or feet, and 1 isolated De Quervain's tenosynovitis. Of the 5 patients with arthritis, 3 also had episodes of swelling with pitting edema over the dorsum of hands and/or feet together with flexor digit tenosynovitis, 2 also had olecranon bursitis, and 1 tibial tenosynovitis. No patient had clinical or radiological manifestations of spondyloarthritis. None had the HLA-B27.

Conclusion. In Italian Caucasian patients with WD there was no association with spondyloarthritis and HLA-B27. (J Rheumatol 2001;28:1294–7)

Key Indexing Terms:
WHIPPLE'S DISEASE SPONDYLOARTHROPATHIES MHC ANTIGENS

Whipple's disease (WD) is a rare systemic infection caused by a bacterium just recently cultivated[1]. The disease is characterized by fever, diarrhea, steatorrhea, wasting, and a variety of extraintestinal manifestations including lymphoadenopathy, endocarditis, and musculoskeletal and neurological involvement.

Peripheral arthritis is very frequent in WD and may appear many years before the intestinal complaints and other symptoms[2]. In 1974 Moll and Wright suggested that WD should be included among the seronegative spondyloarthropathies (SpA) on the basis of some studies suggesting a higher frequency of sacroiliitis and ankylosing spondylitis (AS)[3]. Subsequent studies on the frequency of axial involvement and the frequency of HLA-B27 have shown conflicting results[4-10]. Therefore the inclusion of the disease in the SpA complex is still controversial.

The clinical spectrum of SpA has been broadened considerably in the last few years[11]. In addition to the definite forms, there are others called undifferentiated SpA resulting from the various combinations of clinical and radiological manifestations of the B27 associated disease process[11]. Classification criteria for SpA have been proposed with the aim to encompass their wide clinical spectrum, including the undifferentiated forms[12].

We examined a consecutive series of Italian patients with WD for the full clinical spectrum of SpA.

From the Rheumatology Department of Lucania, S. Carlo Hospital, Potenza; the Institute of Hematology and Medical Oncology L.A. Seragnoli; the Clinical Pathology Department and the Department of Internal Medicine and Gastroenterology of Sant'Orsola-Malpighi Hospital, Bologna; and the Department of Gastroenterology, IRCCS, Policlinico San Matteo, Pavia, Italy.

Drs. Olivieri and Padula's work was supported by a research grant from the Government of Basilicata (Lucania) Region.

I. Olivieri, MD, Consultant; A. Padula, MD, Researcher, Rheumatology Department of Lucania; G. Brandi, MD, PhD, Researcher; G. Biasco, MD, Associate Professor of Medical Oncology, Institute of Hematology and Medical Oncology L.A. Seragnoli, Policlinico Sant'Orsola-Malpighi, Bologna University;

M. Di Stefano, MD, Fellow; G.R. Corazza, MD, Professor of Gastroenterology, Department of Gastroenterology, IRCCS, Policlinico San Matteo; W. Mantovani, PhD, Clinical Pathology Department, Policlinico Sant'Orsola-Malpighi; C. Calabrese, MD, Fellow; G. Saccoccio, MD, Fellow; G. Di Febo, MD, Associate Professor of Gastroenterology; M. Miglioli, MD, Professor of Internal Medicine, Department of Internal Medicine and Gastroenterology, Policlinico Sant'Orsola-Malpighi, Bologna University.

Address reprint requests to Dr. I. Olivieri, Rheumatology Department of Lucania, Ospedale S. Carlo, Contrada Macchia Romana, 85100 Potenza, Italy. E-mail: ignazioolivieri@tiscalinet.it

Submitted July 21, 2000 revision accepted December 6, 2000.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2001. All rights reserved.

Downloaded on April 17, 2024 from www.jrheum.org

MATERIALS AND METHODS

Nine consecutive patients in whom WD was diagnosed with duodenal biopsy in the University Hospital of Bologna were clinically evaluated and examined for clinical and radiological manifestations of SpA by 2 rheumatologists with expertise in this field (IO, AP). Patients were seen over a 5 year period and were all living in Emilia and Romagna in the north of Italy.

Eight patients were male and one female. Their mean age at the time of study and at diagnosis of WD by intestinal mucosal biopsy were 62.4 years (42–71) and 54.4 years (range 40–62), respectively (Table 1). The mean interval between diagnosis and this study was 8 years (range 1–19) and between the onset of symtoms and this study 14.5 years (6–25). Each patient had received adequate antibiotic therapy. All clinical manifestations of WD had been carefully registered in the patient's chart at the time of the initial diagnosis. All the medical records of the patients were also reviewed.

The day of study examination each patient was questioned about peripheral joint and enthesis symptoms, dactylitis, chest wall pain, inflammatory spinal pain, buttock pain, ocular symptoms of uveitis and conjunctivitis, cutaneous and mucous symptoms, and gastrointestinal and urogenital symptoms. Patients were also questioned about family history of SpA and other HLA-B27 associated diseases and Behçet's disease.

Each patient had a complete clinical examination, including examination of their spine, peripheral entheses and joints, and skin and mucosae. Anterior flexibility of the lumbar spine was measured using the Macrae and Wright modification of the Schober test[13] and chest expansion was measured in the 4th intercostal space. Previous peripheral arthritis, peripheral enthesitis, dactylitis (flexor tenosynovitis with the sausage-like swelling of the whole digit), tenosynovitis, bursitis, and inflammatory swelling with pitting edema of the dorsum of hands and feet were taken into account only if diagnosed and documented by a physician.

Class I and Class II alleles were determined in all patients using a modification of the 2 stage National Institutes of Health complement microcytotoxicity test[14]. The healthy control group consisted of a pool of 242 blood donor volunteers from the same geographic area.

Each patient had an anteroposterior radiographic view of the pelvis. Pelvic films were randomized and mixed with those of 10 control subjects with mechanical low back pain and examined blindly and independently by the 2 rheumatologists. Each sacroiliac (SI) joint was scored separately using the New York criteria[15]. Radiographs on which the observers were in disagreement were examined again together and a reconciled score was established. If suspicious (grade 1) or grade 2 sacroiliitis was observed, a computed tomography (CT) of the SI joints was performed for better definition of sacroiliac joints.

RESULTS

Eight of the 9 patients had rheumatogical manifestations related to WD that had begun 6.1 years (range 1–15) before diagnosis of disease by intestinal biopsy (Table 1). The rheumatological manifestations were recurrent and self-limiting in all patients. Patient 1 had recurrent episodes of polyarthritis involving shoulders, elbows, wrists, carpi, proximal hand interphangeal (PIP) joints, knees, ankles, and tarsi. Patient 4 had episodes of oligoarthritis involving wrists, carpi, and knees. Patients 2, 3, and 5 had recurrent episodes of monoarthritis. Patients 7 and 8 only had episodes of synovitis showing swelling with pitting edema of the dorsum of hand suggesting involvement of the synovial sheaths of the extensor tendons. Patient 9 only had a severe bilateral abductor pollicis longus and extensor pollicis brevis tenosynovitis (De Quervain's tenosynovitis) for one month. Synovitis with

Table 1. Rheumatologic manifestations in the 9 patients with WD.

Patient	Sex	Present Age, yrs	Age at Arthritis Onset, yrs	Age at WD Diagnosis, yrs	Rheumatologic Manifestation
1	M	42	35	40	Polyarthritis involving shoulders, elbows, wrists, carpi, PIP joints, knees, ankles, tarsi. Synovitis with swelling showing pitting edema of the dorsum of hands and feet with sausage-like swelling of some fingers and the first toe
2	M	63	43	44	Episodes of monoarthritis of ankles and knees. Episodes of 1 week duration of synovitis with swelling showing pitting edema of the dorsum of hands with sausage fingers. Episodes of 2 wk duration of tibial tenosynovitis
3	M	64	39	48	Episodes of 1 wk duration of wrist monoarthritis Episodes of 1 wk duration of olecranon bursitis
4	M	71	56	60	Episodes of 1 wk duration of oligoarthritis of wrists and knees and of synovitis with swelling with pitting edema of the dorsum of hands. Episodes of olecranon bursitis
5	M	59	53	55	Recurrent episodes of 3–7 days duration of monoarthritis of ankles and wrists
6	M	66		60	—
7	F	63	48	63	Episodes of 3–6 day duration of synovitis with swelling showing pitting edema of the dorsum of hands extending to the wrist and the proximal part of the extensor surface of the forearm
8	M	62	51	58	Three episodes of 10 month duration of swelling with pitting edema of the dorsum of the left hand
9	M	71	57	62	Bilateral De Quervain's tenosynovitis of 1 mo duration

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2001. All rights reserved.

Downloaded on April 17, 2024 from www.jrheum.org

swelling with pitting edema over the dorsum of hands and/or feet was also observed in Patients 1, 2, and 4. During some of these episodes, Patients 1 and 2 had also sausage-like fingers and/or toes suggesting the involvement of synovial sheaths of the digit flexor tendons. Patient 2 also had tenosynovis of the tibial tendons and Patients 3 and 4 olecranon bursitis.

Only one patient (Patient 1) had rheumatological manifestations on the day of the rheumatological assessment. He showed arthritis of the 3rd PIP joint of the right hand that persisted afterwards. No patient showed any limitation of spine mobility or chest expansion.

No patient had a family history of SpA, HLA-B27 associated diseases, or Behçet's disease. Moreover no patient had ever had clinical manifestations of SpA such as peripheral enthesitis, inflammatory spinal pain, chest wall pain, or uveitis. Patient 6 had a history of skin lesions for a few months diagnosed as psoriasis by a dermatologist 10 years before the current examination.

All patients had normal SI joints on plain radiographs, so there was no need to perform CT of these joints. No patient had HLA-B27 or one of the B7-CREG antigens (Table 2). No patient had positive tests for rheumatoid factors or antinuclear antibodies. The phenotype frequency of HLA-B27 in blood donors was 2.4%.

DISCUSSION

The results of our study confirm that the rheumatological manifestations of WD are very frequent and appear years before other complaints of the disease. Eight of 9 patients had peripheral arthritis that had appeared 1 to 15 years before diagnosis of WD. In accordance with the literature, arthritis was recurrent and not destructive. The recurrent episodes were polyarticular, oligoarticular, and monoarticular. Except for the longer duration, the recurrent monoarthritis in our patients had findings suggestive of palindromic rheumatism. The possibility that peripheral arthritis of WD may begin and evolve as palindromic rheumatism has recently been emphasized[16].

Our study suggests that peripheral synovial inflammation in WD may involve bursa and tendon sheath synovium in addition to joint synovium. One patient had tibial tenosynovitis and two olecranon bursitis. Five patients had swelling of the dorsum of hands and/or feet, which has been reported in several rheumatologic conditions including remitting seronegative symmetrical synovitis with pitting edema (RS_3PE) syndrome, polymalgia rheumatica, psoriatic arthritis, and late onset SpA[17]. We previously reported, using magnetic resonance imaging, that the subcutaneous edema on the hand and foot dorsum is due to altered permeability as a consequence of extensor tenosynovitis[18]. Patients 1 and 2 had sausage-like digit in addition to the swelling on the dorsum of the hand or foot. We recently reported that the sausage-like swelling in SpA is due to flexor tenosynovitis[19], which may have caused the sausage-like swelling also in our patients with WD. However, the occurrence of swelling of the dorsum with pitting edema and sausage-like digit cannot be considered as proof for the inclusion of WD in the SpA complex. Our patients did not develop other typical SpA manifestations such as peripheral enthesitis and axial involvement; and they had a negative family history for SpA and did not possess the HLA-B27.

The inclusion of WD in the SpA complex was suggested by Moll and Wright in 1973 on the basis of some previous studies suggesting a higher frequency of sacroiliitis and AS[2]. In 1963 Kelly and Weisinger reevaluated the arthritis of WD and found that AS had been diagnosed in 18 patients[20]. However, Moll and Wright could agree with the diagnosis of AS in only 4 of these 18 patients[21]. Subsequently, several cases of coexisting WD and AS have been reported[4,5]. Only a few studies have examined consecutive patients with WD for sacroiliitis and AS[6,7]. In none of them was reading of SI joints performed blindly to reduce observer error. D'Eshougues, *et al* found 5 patients with sacroiliitis among 18 with WD[6]. Khan studied 6 patients with WD and found 1 with AS[7]. Four of these patients were HLA typed and all 4 lacked HLA-B27. In 1979 Feurle, *et al* performed HLA typing in 9 patients with WD without sacroiliitis and AS and found B27 in 4[8]. They suggested that WD may be associated with B27. Similar conclusions were issued by Dobbins in 1987 after reviewing world literature[9]. Thirteen (28%) of 48 patients typed for the B27 antigen were positive. Twelve of the 48 were described as having sacroiliitis and only 2 of them were B27 positive. A limitation of the Dobbins study was that data were obtained from different geographic areas and from different laboratories. In 1991, Blai, *et al* performed HLA typing in 14 Argentinian patients with WD and compared the frequency of B27 with that of blood donors from the same geographic area typed in the same laboratory[10]. The frequency was 7.7% in patients with WD and 4% in controls. Our study was performed similarly and no higher frequency of the B27 antigen was found in patients with WD. In addition we studied our patients for the full clinical spectrum of SpA and examined radiographs of the SI joints blindly. No patient was found to be affected by SpA in spite of the longer duration of the interval between onset of WD and rheumato-

Table 2. HLA typing of the 9 patients with WD.

	HLA Type				
	A	B	C	DR	DQ
Patient					
1	11,24	49,X	XX	13,16	1
2	26,30	8,38	w7	11,13	1,7
3	26,30	13,38	w6	3,7	2
4	2,X	57,49	w6,w7	11,52	1,2
5	10,33	35,51	w2	2,11	1,3
6	24,33	55,65	XX	4,11	3
7	1,33	8,14	w7,w8	7,13	1,2
8	2,3	35,39	W4,w7	14,15	1,5
9	1,24	60,63	W3,w7	3,16	1,2

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2001. All rights reserved.

Downloaded on April 17, 2024 from www.jrheum.org

logical evaluation in comparison with other studies. Similarly to the study by Bai, *et al* no association was found with other class I and II HLA antigens. As people of Italian descent account for up 60% of the Argentinian population, it would be of great interest to know the heritage of the Argentinian patients studied by Bai and co-workers.

Our study, although carried out on a restricted number of patients, does not support the inclusion of Whipple's disease in the SpA group of diseases. We hope other studies will be performed in other ethnic groups in the near future. Another approach to exclude definitively the association of WD with SpA is to obtain bacteriological data on *Tropherima whippelii* in a larger series of patients with SpA.

ACKNOWLEDGMENT

We thank Muhammad Asim Khan for critical revision of the manuscript.

REFERENCES

1. Raoult D, Birg ML, La Scola B, et al. Cultivation of the bacillus of Whipple's disease. New Engl J Med 2000;342:620-5.
2. Wollheim FA. Enteropathic arthritis. In: Kelly WN, Ruddy S, Harris ED Jr, Sledge CB, editors. Textbook of rheumatology. 5th ed. Philadelphia: WB Saunders; 1997:1006-14.
3. Moll JM, Haslock I, Macrae IF, Wright V. Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies, and Behçet's disease. Medicine (Baltimore) 1974;53:343-64.
4. Canoso JJ, Saini M, Hermos JA. Whipple's disease and ankylosing spondylitis: simultaneous occurrence in HLA-B27 positive male. J Rheumatol 1978;5:79-84.
5. Blaison D, Carteret E, Renard P, et al. Un cas de maladie de Whipple avec spondylarthrite ankylosante traité par triméthoprime-sulfaméthoxazole [A case of Whipple's disease with ankylosing spondylitis treated with trimethoprim-sulfamethoxazole]. Ann Gastroentérol Hépatol 1991;27:51-5.
6. D'Eshougues R, Delcambre B, Defrance D. Les manifestations articulaires de la maladie de Whipple [Articular manifestations of Whipple's disease]. Rev Rhum 1976;43:565-73.
7. Khan MA. Axial arthropathy in Whipple's disease. J Rheumatol 1982;9:928-9.
8. Feurle GE, Dorken B, Schopf E, Lenhard V. HLA-B27 and defects in T-cell system in Whipple's disease. Eur J Clin Invest 1979;9:385-9.
9. Dobbins WO III. HLA antigens in Whipple's disease. Arthritis Rheum 1987;30:102-5.
10. Bai JC, Mota AH, Mauriño E, et al. Class I and Class II HLA antigens in a homogeneous Argentinian population with Whipple's disease: lack of association with HLA-B 27. Am J Gastroenterol 1991;86:992-4.
11. Khan MA, van der Linden SM. A wider spectrum of spondyloarthropathies. Semin Arthritis Rheum 1990;20;107-13.
12. Dougados M, van der Linden S, Juhlin R, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum 1991;34:1218-27.
13. Macrae IF, Wright V. Measurement of back movement. Ann Rheum Dis 1969;28:584-9.
14. Terasaki P, McClelland JD. Microdoplet assay of human cytotoxins. Nature 1964;204:998-1000.
15. Bennett PII, Wood PHN. Population studies of the rheumatic diseases. Proceedings of the Third International Symposium, New York, June 1966. Amsterdam: Excerpta Medica Foundation; 1968:456-7.
16. Berthelot JM, Dao T, Brégeon C, Maugars Y, Prost A. Rhumatisme palindromique révélateur de maladie de Whipple: etude à partir de deux cas personnels [Palindromic rheumatism with evidence of Whipple's disease: 2 cases]. Rev Rhum [Ed Fr] 1994;61:44-8.
17. Olivieri I, Salvarani C, Cantini F. Remitting distal extremity swelling with pitting edema: a distinct syndrome or a clinical feature of different inflammatory rheumatic diseases? J Rheumatol 1997;24:249-52.
18. Cantini F, Salvarani C, Olivieri I, et al. Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome: a prospective follow-up and magnetic resonance study. Ann Rheum Dis 1999;58:230-6.
19. Olivieri I, Barozzi L, Favaro L, et al. Dactylitis in patients with seronegative spondylarthropathy: assessment by ultrasonography and magnetic resonance imaging. Arthritis Rheum 1996;39:1524-8.
20. Kelly JJ, Weisinger BB. The arthritis of Whipple's disease. Arthritis Rheum 1963;6:615-32.
21. Wright W, Moll J. Seronegative polyarthritis. Amsterdam: North Holland Publishing; 1976.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2001. All rights reserved.

Downloaded on April 17, 2024 from www.jrheum.org