60-66 *Clinical rheumatology*, 1987, **6**, Suppl. N° 2

Outcome of possible ankylosing spondylitis in a 10 years' follow-up study

W. MAU*, H. ZEIDLER**, R. MAU*, A. MAJEWSKI°, J. FREYSCHMIDT°°, H. DEICHER*

*Department of Internal medicine and Dermatology, Medical School Hannover, W.-Germany, **Department of Internal Medicine, University Hospital Düsseldorf, W.-Germany, °Department of Radiology, Medical School Hannover, W.-Germany, °°Department of Radiology, Central Hospital St.-Jürgen-Straβe, Bremen, W.-Germany.

SUMMARY *Of 88 selected patients with possible ankylosing spondylitis (AS) 54 (61%) participated in two phases of a 10 years' follow-up study. Thirty-two (59%) developed definite AS according to the New York criteria, 10 (19%) had possible/undifferentiated seronegative spondylarthropathy (SSA) and 12 patients had other diagnoses. Only 3 (9%) of 35 patients with sacroiliitis did not fulfill the New York criteria for definite AS until the last examination. Sacroiliitis and radiological spinal signs of AS appeared rather late above a mean age of 40 years and after a mean disease duration of more than 10 years. After 18 years mean disease duration 25 (78%) of 32 AS patients had good or sufficient functional capacity indicating an overall good functional prognosis. HLA B27 typing proved to be useful in patients with possible early AS: 29 (71%) of 41 B27 positive and 3 (23%) of 13 B27 negative patients developed definite AS ($p < 0.005$). A combination of the B27 test with data of the history, clinical, laboratory, and radiological examination proposed as early diagnostic criteria detected patients with the outcome diagnosis of definite AS with even higher significance ($p < 0.001$). These criteria were also useful in the identification of patients with possible or undifferentiated SSA. The recently recognized entity of undifferentiated SSA should only be diagnosed after long term follow-up.*

Key words: Follow-Up Study, Possible Ankylosing Spondylitis, Sacroiliitis, Prognosis, HLA B27, Early Diagnostic Criteria.

INTRODUCTION

After which period of time should the diagnosis of ankylosing spondylitis (AS) be ruled out in patients with certain risk factors? Clinicans don't know the answer to this question. Only a few follow-up studies of patients with seronegative peripheral arthritis and possible AS have been carried out (1-6). As these patients were usually followed only for a short time, the true incidence of axial involvement during the course of the disease is not known. Therefore we prolonged the observation period of patients

Correspondence to: Dr. W. MAU,
Division of Rheumatology, Department of Internal Medicine and Dermatology, Medical School Hannover, Konstanty-Gutschow-Straβe 8, D-3000 Hannover 61, W.-Germany.

Table I *Data at first examination of the selected and available patients with possible AS*

Data at first examination	Selected n = 88	Available after phase I n = 66 (75%)	Available after phase II n = 54 (61%)
Mean age (± standard dev.)	38 ± 11	39 ± 12	38 ± 10
Sex ratio (f : m)	1 : 1.9	1 : 1.9	1 : 2
HLA B27 positive	61 (69%)	46 (70%)	41 (76%)
Raised ESR	51 (58%)	34 (52%)	29 (54%)
Low back pain	77 (88%)	56 (85%)	48 (89%)
Heel pain	19 (22%)	13 (20%)	11 (20%)
Peripheral arthritis	53 (60%)	37 (56%)	28 (52%)
Anterior uveitis	13 (15%)	8 (12%)	8 (15%)
Normal X-rays of the sacroiliac joints	50 (57%)	37 (56%)	27 (50%)
Suspicious X-rays of the sacroiliac joints	38 (43%)	29 (44%)	27 (50%)

with a possible early stage of AS to more than one decade (see Ref. 7 for results of our 5-6 years follow-up study). We wanted to assess the timing of the disease progression, the severity of the disease, and the diagnostic value of the HLA B27 typing result in the context of clinical data.

PATIENTS AND METHODS

Eighty-eight patients with possible AS were selected for this follow-up study because of low back pain, peripheral arthritis, heel pain, anterior uveitis or raised ESR (Table I). They had normal or suspicious X-rays of the sacroiliac joints. Patients with unequivocal sacroiliiitis were excluded from the study. After phase I (5-6 years) 66 patients (75%) were available for a complete clinical, radiological, and laboratory reexamination and after phase II (10-11 years from study start) 54 of these patients (61%) were examined again. The available group was representative of the selected sample concerning mean age, sex, HLA B27, and the selection criteria mentioned above.

Standard X-rays in two planes were taken

Table II *Early diagnostic criteria for ankylosing spondylitis*

	Criteria	Points
Genetic	– HLA B27 positive	1.5
Clinical	– Spine pain (inflammatory type)	1
	– Low back pain spontanous or elicited by stress tests of sacroiliac joints	1
	– Thoracic pain spontanous or produced by compression or limited chest expansion ($\leqslant$ 2.5 cm)	1
	– Peripheral arthritis or heel pain	1
	– Anterior uveitis	1
	Limited motion of cervical or lumbar spine in all planes	1
Laboratory	– Raised ESR: age < 50: m > 15 mm/h, f > 20 mm/h; age $\geqslant$ 50: m > 20 mm/h, f > 30 mm/h	1
Radiological	– Spinal signs: syndesmophytes/squarring phenomenon/barrel-shaped vertebra/Romanus or Anderson lesions/involvement of apophyseal or costovertebral joints	1

A total count of $\geqslant$ 3.5 points indicates early ankylosing spondylitis.

of the pelvis and the lumbar spine in all patients at the start of the study, after phase I, and after phase II. For radiological evaluation of the entire spine additional X-rays in two planes were taken of the cervical and thoracic spine in all patients at the end of the study. All films were read by two radiologists without knowledge of the clinical data and the HLA B27 typing result. Grading of sacroiliitis and definite diagnosis of AS were based on the New York criteria (8). Rheumatoid arthritis was diagnosed according to the ARA criteria (9). For early diagnosis of AS we applied a more practicable modification of early diagnostic criteria previously proposed by Baudoin and Landureau (10) (Table II) to the data of the first examination.

For evaluation of disability we attached the patients with definite AS to four classes of functional capacity similar to the classification of rheumatoid arthritis patients proposed by Steinbrocker (11).

Table III *Outcome diagnoses of all patients with possible ankylosing spondylitis (AS) after phase I (5-6 years) and after phase II (10-11 years from study start)*

	After phase I + n = 66 (12)	After phase II n = 54
Definite AS	24 (−) 36%	32 59%
Possible or undifferentiated SSA	28 (4) 43%	10 19%
Rheumatoid arthritis	4 (4) 6%	–
Unclassified arthritis	1 (−) 1.5%	–
Psoriatic arthritis	–	2
Degenerative spine disease/fibromyalgia	8 (3) 12%	9 } 12
Selflimited rheumatic disease	1 (1) 1.5%	1 } 22%

+ Number of patients not available after phase II in parentheses.

RESULTS

After phase I 24 (36%) and after phase II 32 patients (59%) fulfilled the New York criteria for definite AS (Table III). After phase I 28 (43%) had still possible or undifferentiated seronegative spondylarthropathy (SSA), 4 of these patients were lost during phase II, 3 of them showing grade 2 or 3 sacroiliitis. Ten patients (19%) were judged as possible or undifferentiated SSA at the end of the study. Four patients with definite rheumatoid arthritis according to the ARA criteria and 1 patient with unclassified arthritis after phase I were lost during further follow-up. At the end of the study 12 patients (22%) had other diagnoses: 2 had psoriatic arthritis, 9 degenerative spine disease or fibromyalgia and one patient had no signs of persisting rheumatic disease.

Table IV shows demographic data and HLA B27 frequency in the three main

Table IV *Demographic data and HLA B27 in the main groups of outcome diagnosis after phase II of the follow-up*

	AS n = 32	Possible/undifferentiated SSA n = 10	Other diagnosis n = 12
Sex ratio (f:m)	1 : 3	1 : 1.5	1 : 1
Mean age at disease onset	31 ± 9	23 ± 11	30 ± 8
Mean disease duration	8 ± 6	8 ± 7	10 ± 10
HLA B27 positive	29 (91%)	8 (80%)	4 (33%)+

+ Chi-square = 15.78 by 3×2 table, $p < 0.001$

Table V *Progression of all patients with initial diagnosis of possible AS in relation to the sacroiliitis grade*

	Grade of sacroiliitis				
	0	1	2	3	4
At study start	27 (9)$_{+}$	27 (23)	–	–	–
After phase I	20 (3)	7 (3)	6 (5)	19 (19)$_{a)}$	2 (2)
After phase II	13 (–)	6 (–)	8 (5)$_{b)}$	19 (19)$_{c)}$	8 (8)$_{d)}$

$^{+}$Number of patients with outcome diagnosis of definite AS in parentheses
Asymmetric sacroiliitis: a) 3/0 (n = 2), b) 1/2 (n = 2), c) 2/3 (n = 2), d) 3/4 (n = 1)

groups of outcome diagnoses. The sex ratio females: males was 1:3 in AS, 1:1.5 in patients with possible or undifferentiated SSA, and 1:1 in other diagnoses. We found a similar high frequency of the HLA B27 antigen in AS and possible or undifferentiated SSA (91%, 80% respectively), whereas only 33% of patients with other diagnoses were B27 positive ($p < 0.001$).

Looking for the progression of patients in relation to sacroiliitis during follow-up (Table V) we found 23 (85%) of 27 patients with suspicious sacroiliac joints at study start developing definite AS compared with 9 (33%) of 27 with normal X-rays ($p < 0.001$). Only 3 (9%) of 35 patients with grade 2-4 sacroiliitis did not fulfill the New York criteria for definite AS until the last examination.

By dividing the follow-up study in two phases we were able to define the intervall of age and disease duration of the first appearance of radiological signs in our AS patients (Table VI). Unequivocal sacroiliitis (at least grade 2) developed between a mean age of 40 and 45 years and after 9 to 14 years mean disease duration. The first manifestation of typical radiological spinal signs was seen between a mean age of 41 and 46 years and after 11 to 16 years mean duration of the disease. Four patients had positive spinal X-rays already at the start of the study prior to unequivocal sacroiliitis and 4 patients had still normal spinal radiographs after phase II.

For evaluation of disability we attached the patients with definite AS to four classes of functional capacity similar to the classification of rheumatoid arthritis patients proposed by Steinbrocker (11) (Table VII). No patient reached class IV and only 7 males (22%) class III after a mean disease duration of 18 years. Twenty-four patients (78%) had a good or sufficient functional capacity

Table VI *Mean age and disease duration (± standard deviation) of all patients with outcome diagnosis of definite AS at last examination without sacroiliitis/radiological spinal signs and at first examination proving sacroiliitis/radiological spinal signs indicating the intervall of the development of these radiological changes.*

	At last examination without sacroiliitis	At first examination proving sacroiliitis (⩾ grade 2)	At last examination without radiological spinal signs	At first examination with radiological prove of spinal signs	Radiological spinal signs at study start	No radiological spinal signs after phase II
	n = 32	n = 32	n = 24	n = 24	n = 4	n = 4
Mean age	40 ± 9	45 ± 9	41 ± 8	46 ± 8	45 ± 14	46 ± 3
Mean disease duration	9 ± 6	14 ± 6	11 ± 6	16 ± 6	11 ± 5	14 ± 5

Table VII *Follow-up data in relation to classes of functional capacity in patients with outcome diagnosis of definite AS*

	Functional capacity of AS patients after phase II			
	Class I n = 8 (25%)	Class II n = 17 (53%)	Class III n = 7 (22%)	Total n = 32
Mean age at onset (± stand. dev.)	30 ± 6	29 ± 8	37 ± 11	31 ± 9
Mean disease duration (± stand. dev.)	19 ± 7	18 ± 6	18 ± 6	18 ± 6
Sex ratio (f : m)	1 : 1.7	1 : 2.4	0 : 7	1 : 3
HLA B27 negative	1 (12%)	1 (6%)	1 (14%)	3 (9%)

Table VIII *Demographic, clinical, and radiological data of patients with the outcome diagnosis possible or undifferentiated SSA*

Demographic and clinical data after phase II	Diagnosis after phase II	
	Possible SSA n = 6	Undifferentiated SSA n = 4
Mean age at onset (± standard dev.)	19 ± 11	31 ± 6
Mean disease duration (± standard dev.)	13 ± 2	24 ± 7
Sex ratio (f : m)	2 : 1	0 : 4
HLA B27 positive	6	2
Low back pain	4	4
Heel pain	2	3
Family history of AS	3	–
Peripheral arthritis	5	3
Sacroiliitis (grade 0 / 1/2)	1/2/3	–/4/–
Typical radiological spinal signs of AS	–	2

Table IX *Comparison of the diagnostic tests at study start in relation to the final diagnosis of definite ankylosing spondylitis*

	Ankylosing spondylitis after phase II		Statistical evaluation
	Yes (n = 32)	No (n = 22)	
HLA B27 positive	29	12	Chi-square = 7.42 $p < 0.01$
HLA B27 negative	3	10	
Early diagnostic criteria without HLA B27 positive	30	15	Chi-square = 5.74 $p < 0.05$
Early diagnostic criteria without HLA B27 negative	2	7	
Early diagnostic criteria including HLA B27 positive	28	9	Chi-square = 11.05 $p < 0.001$
Early diagnostic criteria including HLA B27 negative	4	13	

Table X *Comparison of three diagnostic tests at study start in relation to the final diagnosis of definite ankylosing spondylitis after phase II (10-11 years follow-up) in statistical terms*

	Sensitivity	Specificity	Predictive value of positive test	Predictive value of negative test
HLA B27 test	91%	45%	71%	77%
Early diagnostic criteria without HLA B27 test	94%	32%	67%	78%
Early diagnostic criteria including HLA B27 test	88%	59%	76%	76%

(class I and II) after almost the same duration of the disease (19 years, 18 years respectively).

Table VIII gives a detailled description of patients regarded as still possible or undifferentiated SSA at last examination. Six HLA B27 positive patients were judged as still possible SSA because of high frequency of low grade sacroiliitis, positive family history of AS in combination with similar symptoms as in AS at comparatively young age and short disease duration. Four older male patients with long disease duration could not be classified with one of the well established diagnoses. They had several features in common with AS patients including typical radiological spinal signs in two patients. All had grade I sacroiliitis and low back pain. These patients were judged as undifferentiated SSA, a recently recognized new nosological entity (12,13), characterized as a combination of low back pain, peripheral often asymmetrical arthritis, heel pain, minimal sacroiliitis and high HLA B27 association.

We tried to increase the chance of a correct early diagnosis of AS by combining the result of the B27 test with data of the history, clinical, laboratory, and radiological examination. For this purpose we used a more practicable modification of early diagnostic criteria previously proposed by Baudoin and Landureau (10) (Table II). These criteria were applied to the data of the first examination. We compared the diagnostic values of three tests: HLA B27 test alone, early diagnostic criteria without HLA B27, and early diagnostic criteria including HLA B27 (Table IX). Early diagnostic criteria including HLA B27 reached the highest discriminating significance regarding the development of definite AS according to the New York criteria ($p < 0.001$). These criteria had only a slightly lower sensitivity of 88% but a higher specificity of 59% and positive predictive value of 76% compared with the

Table XI *Frequencies and mean scores of early diagnostic criteria at first examination and during follow-up in relation to outcome diagnoses*

Early diagnostic criteria	Outcome diagnosis		
	Definite AS (n = 32)	Possible or undifferentiated SSA (n = 10)	Other diagnoses (n = 12)
At first examination			
⩾ 3.5 points	28 (88%)	6 (60%)	3 (25%)
mean score (± standard deviation)	4.5 ± 1 P	3.5 ± 1.5 P	2.5 ± 1.5 P
During follow up			
⩾ 3.5 points	32 (100%)	7 (70%)	3 (25%)
mean score (± standard deviation)	7 ± 1.5 P	4.5 ± 1.5 P	2.5 ± 1.5 P

other two tests (Table X). The negative predictive value was almost the same in the three tests (76%-78%). So in more than three quarters of cases early diagnostic criteria did correctly indicate or exclude AS in our selected group of patients with possible AS at an early stage of the disease.

In these calculations it has to be kept in mind that "non AS patients" include 10 patients with still possible or undifferentiated SSA after phase II. At study start they had a higher mean score of 3.5 P than patients with other diagnoses with 2.5 P ($p < 0.05$) (Table XI). During follow-up their mean score increased to 4.5 P whereas the score of patients with other diagnoses remained unchanged below the cut point (2.5 P).

CONCLUSIONS

Only a few patients with sacroiliitis did not progress to definite AS (New York criteria) until the last examination. Sacroiliitis and radiological spinal signs of AS appeared rather late during the course of the disease. Therefore the diagnosis of AS should not be excluded to early. The majority of AS patients had a good or sufficient functional capacity indicating a good functional prognosis. HLA B27 determination proved to be useful in patients with possible early AS. The combination of the HLA B27 typing result with clinical data proposed as early diagnostic criteria was more valuable than clinical criteria or HLA B27 test alone. Early diagnostic criteria were useful in the identification not only of AS patients but also of patients with possible or undifferntiated SSA. Undifferentiated SSA can be detected and should only be diagnosed after long term follow-up.

Acknowledgement: We wish to thank W. Stangel, M.D., from the Histocompatibility Testing Laboratory for HLA B27 typing and Mrs. Lüllemann and Mrs. Mensing for secretarial assistance.

REFERENCES

1. Sambrook, P., McGuigan, L., Champion, D., Edmonds, J., Fleming, A., Portek, I. Clinical features and follow-up study of HLA B27 positive patients presenting with peripheral arthritis. J Rheumatol 1985, 12, 526.
2. Nasrallah, N.S., Masi, A.T., Chandler, R.W., Feigenbaum, S.L., Kaplan, S.B. HLA B27 antigen and rheumatoid factor negative (seronegative) peripheral arthritis. Am J Med 1977, 63, 379.
3. Nissilä, M., Isomäki, H., Kaarela, K., Kiviniemi, P., Martio, J., Sarna, S. Prognosis of inflammatory joint disease. A three-year follow-up study. Scand J Rheumatol 1983, 12, 33.
4. Sany, J., Rosenberg, F., Panis, G., Serre, H., Seignalet, J. Unclassified HLA-B27 inflammatory rheumatic diseases: follow-up of 23 patients. Arthritis Rheum 1980, 23, 258.
5. Zeidler, H., Wagener, P., Eckert, G., Freyschmidt, J., Fritsch, R., Creutzig, H., Deicher, H. HLA-B27 in possible ankylosing spondylitis with peripheral arthritis. Rheumatol Int 1982, 2, 35.
6. Wagener, P., Mau, W., Zeidler, H., Eckert, G., Robin-Winn, M., Deicher, H. HLA-B27 and clinical aspects of ankylosing spondylitis: results of prospective studies. Immunol Rev 1985, 86, 93.
7. Zeidler, H., Mau, R., Mau, W., Freyschmidt, J., Majewski, A., Deicher, H. Evaluation of early diagnostic criteria including HLA-B27 for ankylosing spondylitis in a follow-up study. Z Rheumatol 1985, 44, 249.
8. Bennett, P.H., Burch, T.A. New York Symposion on population studies in the rheumatic diseases. Bull Rheum Dis 1967, 17, 453.
9. Ropes, M.W., Bennett, E.A., Cobb, S., Jacox, R., Jesser, R.
Revision of diagnostic criteria for rheumatoid arthritis. Bull Rheum Dis 1958, 9, 175.
10. Baudoin, P., Landureaux, M. Critères de diagnostic de la pelvospondylite rhumatismale sans atteinte radiologique des sacro-iliaques. Propositions de mise a jour. Rev Rhum 1979, 46, 403.
11. Steinbrocker, O., Traeger, O.H., Battermann, R.C. Therapeutic criteria in rheumatoid arthritis. JAMA 1949, 140, 659.
12. Burns, T., Marder, A., Becks, E., Sullivan, L., Calin, A. Undifferentiated spondylarthritis: a nosological missing link? Arthritis Rheum 1982, 25 (Suppl.), 142.
13. Prakash, S., Mehra, N.K., Bhargava, S., Malaviya, A.N. HLA B27 related unclassifiable seronegative spondylarthropathies. Ann Rheum Dis 1983, 42, 640.