

Ankylosing spondylitis: how diagnostic and therapeutic delay have changed over the last six decades

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Abstract

Objective

Ankylosing spondylitis (AS) is a chronic, progressive, and disabling disease, but the diagnosis is often missed and markedly delayed. An early diagnosis is important to establish a treatment to reduce disability and modify the natural course of disease. The aim of this study was to investigate the diagnostic (DD) and therapeutic (TD) delay according to the decade of diagnosis. The DD and TD correlation with radiological severity score and the new imaging techniques used in diagnosis (magnetic resonance [MRI], computerised tomography, scintigraphy for sacroiliac joints) were also investigated.

Methods

135 AS patients (45 female and 90 male, 36.5±10.2 years old at diagnosis) with disease onset between 1950 and 2008, were investigated; the time from onset to diagnosis (DD) and treatment (TD), the New York and ASAS criteria fulfilment, the New York sacroiliac radiological score, bamboo spine presence at first visit and the new imaging technique used at diagnosis were recorded and their correlations were analysed.

Results

The New York and ASAS criteria were met at the first visit, by 87% and 96%, respectively. The delay from onset of symptoms to diagnosis and treatment was 9±8 and 12±11 years, respectively, but decreased significantly between different decades ($p<0.001$). The severity of sacroiliitis (mean 2±1; 17/135, 12.5% - IV grade sacroiliitis at diagnosis) and bamboo spine (3.7% at diagnosis) correlated with DD and TD ($p<0.001$).

Sacroiliac MRI use at diagnosis significantly decreased both DD and TD ($p>0.001$ and $p<0.05$, respectively).

Conclusions

DD and TD were correlated to radiological severity; they progressively decreased over 6 decades.

Key words

ankylosing spondylitis, axial spondyloarthritis, diagnostic delay, anti-TNF, sacroiliitis

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Background

Ankylosing spondylitis (AS) is a chronic, progressive, and disabling disease characterised by inflammatory back pain, frequently associated to arthritis and enthesitis. AS patients usually develop the most severe spinal modification and peripheral involvement in the first 10 years of disease, with a pattern predictive of the following natural history (1).

In AS, the diagnosis is often missed and delayed because of the interval of 8–11 years on average from onset (2): this delay is due to the fact that patients often do not fulfill the New York criteria because sacroiliitis cannot be detected on x-ray in the early phases of AS (3, 4). Furthermore, before anti-tumour necrosis factor- α blocking agents (anti-TNF- α), treatment options for AS were limited to conventional disease-modifying anti-rheumatic (DMARDs), anti-inflammatory drugs (NSAIDs) and corticosteroids, which have only a limited effect on spinal inflammation. Therefore, in the past, a delayed diagnosis was not considered relevant, even though it led to disability (5) associated to loss of work and depression (6).

Recently, it has been convincingly demonstrated that anti-TNF- α have a strong and prompt effect on almost all features of AS and possibly stop the disease progression by suppressing sacroiliac and spine bone oedema, which is an inflammatory sign detected by magnetic resonance (MRI) (7–8). The response to anti-TNF- α in AS patients has been shown to be more likely in the first 10 years of the disease (9), so an early diagnosis is of the utmost importance for a rapid treatment. Recently, the ASAS group provided a new set of criteria in order to allow an early diagnosis of axial disease; these criteria (ASAS criteria) permit a diagnosis of axial spondyloarthritis using MRI as imaging technique, or even without any radiological assessment (10).

Currently, some studies have shown that the delay was due to the initial incorrect diagnosis of orthopaedists (75.9%), general physicians (50%), but also rheumatologists (12%) (11).

The aim of this study was to evaluate the diagnostic (DD) and therapeutic (TD) delay according to the decade of

diagnosis. As a secondary objective, we assessed the correlation of DD and TD with radiological severity score and different imaging techniques.

Methods

Patients

From March 2009 to July 2009, one hundred and thirty-five AS patients (F:M=45:90, mean age 45.8 ± 12 , range 28–76, mean disease duration 17.9 ± 11 (years), range 1–56) with disease onset (defined by Feldtkeller as first symptoms connected to AS) (12) between 1950 and 2008, were enrolled consecutively from the out-patient clinics of Rheumatology of the two Universities of Florence and Pisa (Italy). The diagnosis was based on the clinician expertise [both using the New York (4) and ASAS criteria for axial spondyloarthritis (10)]. Demographic and clinical data were obtained (from the old records and, occasionally, if missing, from the patients): age and symptoms at onset of AS, age at diagnosis, time between onset and first rheumatologic visit, time between onset and diagnosis (DD), time between onset and first treatment (TD) with DMARDs, NSAIDs, anti-TNF- α and physiotherapy, New York (4) and ASAS criteria (10) positivity at first visit, New York sacroiliac radiological score (4), bamboo spine presence at first visit, new imaging techniques used (MRI, computerised tomography and scintigraphy for sacroiliac joints) at diagnosis.

Initial spondyloarthritis symptoms, that have been assumed as the onset of the disease, were defined as the first onset of, at least, one between inflammatory back pain [both using Calin criteria (13) or based on the clinician expertise when they were not applicable], peripheral or enthesal symptoms, and uveitis.

The differences of DD, TD, imaging techniques and radiological severity between different onset decades (1950, 1960, 1970, 1980, 1990, 2000) were analysed. The correlation of DD and TD with radiological severity and new diagnostic imaging techniques was also calculated.

Statistical analysis

The difference between the decades was evaluated using the Kruskal-Wal-

Competing interests: none declared.

Table I. Demographic, clinical features, DD, TD and New York sacroiliac scores on x-ray in AS patients.

Male / Female ratio		90/45
B27 positive/negative		112 (86.9%) / 33 (13.1%)
Age at onset (<16 years 17/135)		28.3±10.2 (range 9–51 yrs)
Symptoms at onset	<i>Axial involvement</i>	118/135 (87.4%)
	<i>Peripheral arthritis</i>	28/135 (20.7%)
	<i>Enthesitis</i>	7/135 (5.1%)
	<i>Uveitis</i>	4/135 (2.96%)
Age at diagnosis (years)		36.5±12.2 (range 12–73)
Disease duration (years)		17.9±11 (range 1–56)
Delay between onset and first rheumatological visit (years)		8.1±8.2 (range 0–47)
Delay between onset and first sacroiliac x-ray (years)		8.2±7.8 (range 1–47)
Sacroiliac first x-ray New York score		2±1 (range 0–4)
	Score 1: 31/135 (22.9%)	
	Score 2: 61/135 (45.1%)	
	Score 3: 26/135 (19.2%)	
	Score 4: 17/135 (12.5%)	
Delay between onset and diagnosis (DD) (years)		9±8 (range 1–47)
Delay between onset and treatment (TD) (years)		12.45±11.2 (range 1–47)
Delay between onset and anti-TNF- α treatment (years)		12.06±8.8 (range 1–36)
Clinical assessment at diagnosis:	<i>BASDAI (0–100)</i>	34.1±15.2 (range 0–80)
	<i>BASFI (0–100)</i>	24.6±2.1 (range 0–70)
	<i>BASMI (0–10)</i>	2.07±2.08 (range 0–8)
	<i>MASES (0/13)</i>	0.6±1.2 (range 0–12)
	<i>Articular index</i>	0.8±1.2 (range 0–6)

lis test. The correlation of radiological sacroiliitis score with DD and TD was analysed using the Pearson correlation coefficient linear test. The difference of DD and TD between patients with and without presence of bamboo spine and with and without employment of new imaging techniques were evaluated using the Mann-Whitney test.

Means and standard deviations were used to present the data and the level of statistical significance was considered to be lower than 0.05.

Results

Demographic and clinical features, DD and TD of AS patients are shown in Table I.

The delay between the onset and the first rheumatologic visit was 8.1±8.2 years (range 0–47) and, at first visit, 87% and 96% of the patients, respectively, were positive to the New York and the ASAS criteria. New imaging exams were employed at the diagnosis in different percentages: MRI (22/135, 16.2%), scintigraphy (11/135, 8.1%), computerised tomography (7/135, 5.1%).

DD and TD were 9±8 and 12±11 years, respectively; TD was >10 years in 52/135 patients (38.5%) and first treatment was NSAIDs in 105/135 (77.7%),

steroids in 15/135, 11.1%, salazopyrin in 82/135, (60.7%), methotrexate in 12/135 (8.8%), anti-TNF- α in 11/135, 8.1%, physiotherapy in 22/135, 16.3%. Ninety-two out of the 135 patients (68.1%) were treated (during their lifetime) with anti-TNF- α and, more specifically, 64 with Infliximab (47.4%), 15/135 with Adalimumab (11.1%) and 13/135 Etanercept (9.6%). TD for the first anti-TNF- α was 12.06±8.8 years (range 1–36) and >10 years in 43/91 (47.25%).

DD/TD and difference between decades

DD and TD decreased significantly between different decades ($p<0.001$, Kruskal-Wallis). The values of DD and TD for the different decades are shown in Figure 1.

DD/TD:

correlation with radiological damage

At diagnosis, 17 patients (12.5%) had a sacroiliitis grade IV and 5 (3.7%) a bamboo spine. The frequency of the different New York sacroiliac scores on x-ray are shown in Table I.

The presence of x-ray sacroiliac score and bamboo spine correlated positively with DD and TD ($p<0.001$, at Pearson

correlation and $p<0.05$ at Mann-Whitney test, respectively).

DD/TD: correlation with the use of new imaging techniques (MRI, scintigraphy, CT)

The use of MRI for the diagnosis of sacroiliitis increased significantly progressively from 1990 ($p<0.001$), and became more evident in the last few years, when the ASAS group produced the new criteria for the axial spondyloarthritis (14).

DD was significantly lower when sacroiliac MRI ($p<0.01$) and scintigraphy ($p<0.05$) were used for the diagnosis of sacroiliitis, but only sacroiliac MRI use significantly decreased TD and anti-TNF- α -TD ($p<0.05$, Mann-Whitney test).

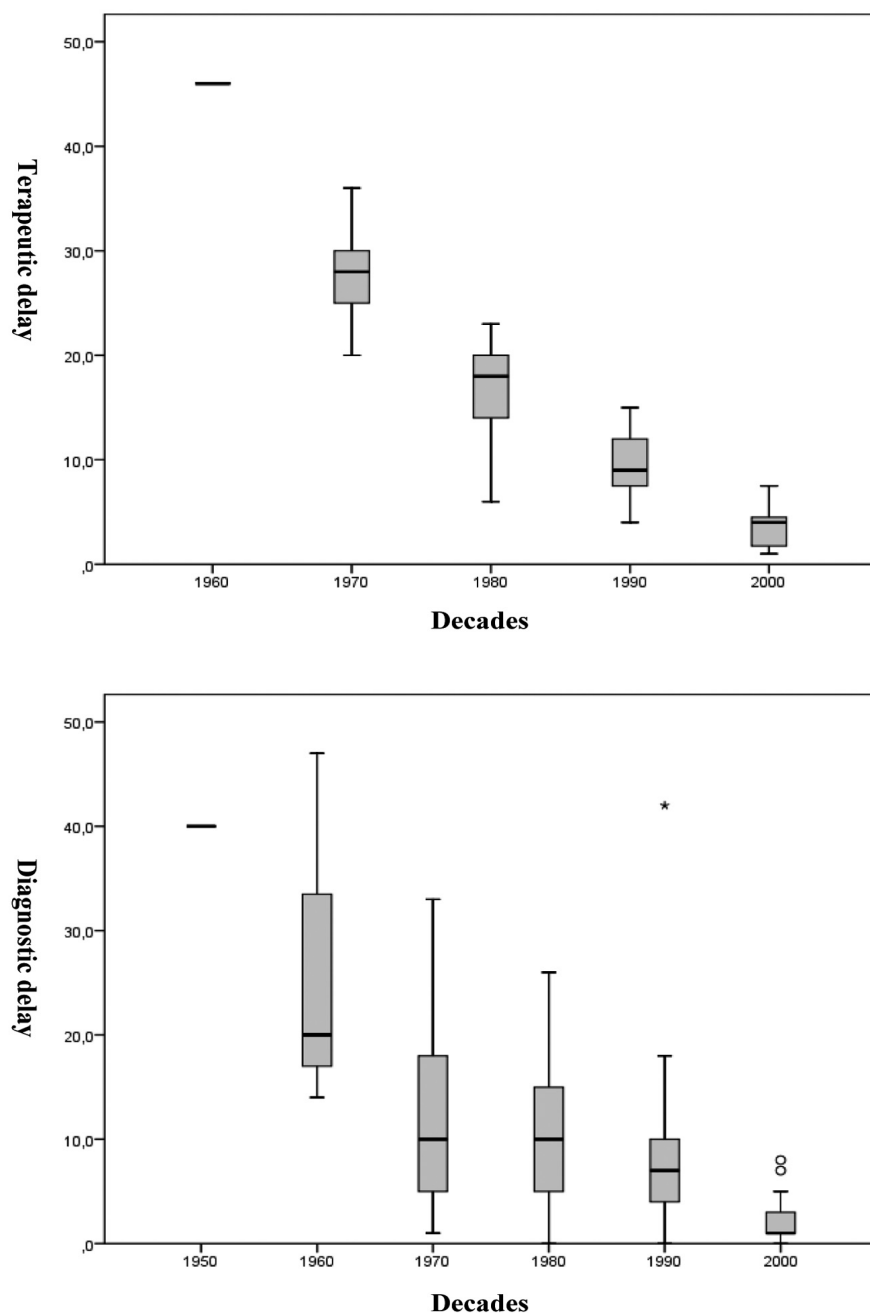
Discussion

Our study, according to previous reports (11, 12, 14), shows a significant DD in a cohort of AS patients. However, the DD was also reduced in the last decades, likely due to the more stringent information delivered to rheumatologists and physicians. Our data showed that in AS patients with DD, the sacroiliac joints and spine radiological damage is severe, as already reported in previous studies (1, 15, 16).

We have observed a DD similar to those in two cohorts of German (12) and Spanish (17) AS patients, while a lower delay was reported in Indian (11) and Turkish (14) populations. In the Aggarwal study (11) disease onset of patients (since 1990) was more recent with respect to our cohort, so it could explain the difference in the results. No evident reasons are given to explain the difference in the other study (14).

A possible explanation for the long DD is the use of the New York criteria that do not allow a definite diagnosis at the onset of symptoms; in fact radiological damage at the sacroiliac joint level is needed, but it can be visualised on x-ray only after several years (18), while the inflammation in early disease could indeed only be detected in recent years by MRI (which is not included in these criteria) (19).

In our study, we demonstrated that DD has progressively decreased over the



	1950	1960	1970	1980	1990	2000
DD	(1) 40	(3) 27±17.58	(14) 12.43±9.90	(34) 10.57±6.55	(49) 7.37±6.20	(34) 2.08±1.91
TD	(1) 42	(3) 33.67±17.39	(14) 19.64±8.40	(34) 11.32±6.51	(49) 7.33±3.84	(34) 2.16±1.89

Fig. 1. Mean, median and standard deviation of DD and TD in the different decades.

last decades, and it is clearly related to the use of MRI and, secondarily, to scintigraphy. The ASAS criteria were evaluated retrospectively because they (the modified ones) were validated only in 2009 and proved to be more

useful than the New York criteria in axial disease. In our experience, the ASAS criteria were positive, at the first rheumatological visit, in a larger part of the patients, with respect to the New York modified criteria, confirming their

higher sensitivity also when used retrospectively in a cohort of patients with a definite diagnosis of AS.

In our study, one of the main causes of DD might be the long delay before the first rheumatologic visit. Previously, general practitioners and non-rheumatologic specialists (*i.e.* orthopaedists, neurosurgeons or internal medicine) had difficulty in recognising AS symptoms and, in particular, inflammatory back pain (14, 20). This delay did not represent a real clue in the past, because of the poor effect of conventional treatment on spinal and sacroiliac inflammation (14, 21) but, after the introduction of anti-TNF- α therapy over the last ten years into routine practice, due to their efficacy (22-24), the pharmacological approach has greatly changed, and nowadays DD represents a very important point as has been shown by the fact that AS patients with shorter disease duration are more likely to respond to anti-TNF agents, overall in the first ten years of disease (9).

Even though the DD (also for anti-TNF- α) was longer than ten years in a large part of our patients, we demonstrated that it diminished in the last six decades. In our cohort the main reason for TD was represented by the delay before the first rheumatologic evaluation and it was negatively influenced by the use of MRI according to the ASAS criteria, which introduced the use of MRI in the diagnostic flow chart (10, 25).

Conclusion

- In AS patients, DD and TD are consistent and correlated with radiological damage
- Their reduction in the last decades is probably correlated with use of MRI to assess sacroiliac inflammation
- The use of ASAS criteria for axial spondyloarthritis allows a more sensitive classification of back pain patients with respect to New York criteria

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