Low frequency of axial involvement in southern Italian Caucasian children with HLA-B27 positive juvenile onset undifferentiated spondyloarthritis

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Abstract

Objectives

To establish how many children with HLA B27-positive juvenile undifferentiated spondyloarthritis (JuSpA) living in southern Italy develop axial disease after 5 years of disease.

Methods

All children with B27-positive enthesitis-related arthritis (ERA) consecutively seen in a 7-year period were entered in a special register and were followed prospectively. Each patient was examined at 6-month intervals, even if asymptomatic. In patients with inflammatory spinal pain and/or buttock pain, MRI of the sacroiliac joints and spine was performed. Five years after inclusion, sacroiliac joint plain radiographs were obtained and read blindly after being mixed with those of control subjects.

Results

Thirteen children, 9 boys and 4 girls, with B27-positive ERA and one girl with B27-positive isolated SpA dactylitis were seen in the study period. Their median age at disease onset and at our first examination were 10 (range 2–16) and 12 years (range 3–16), respectively. During follow-up, only one patient had axial symptoms, i.e. alternate buttock pain. MRI revealed moderate bone oedema at both sacroiliac joints. After five years of disease, no patient showed reduced spinal movement. No sign of sacroiliitis was seen in any patient and control on plain films. A new MRI of the sacroiliac joints of the patient who showed bone oedema in the first years of disease was normal.

Conclusion

This study confirms that the onset of axial involvement in Italian Caucasian HLA-B27 positive children with ERA is rare in the first five years of disease.

Key words

juvenile spondyloarthritis, axial involvement, sacroiliitis, prospective study

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Introduction

Spondyloarthritis (SpA) usually begins in children with a peripheral asymmetric oligoarthritis predominantly involving the lower limbs and/or with peripheral enthesitis and/or with dactylitis (1-21). Most of these children could be classified as undifferentiated SpA (uSpA) (14) according to the Amor (22) and the ESSG criteria (23). In 1982, Rosenberg and Petty recognised the seronegative enthesopathy and arthropathy (SEA) syndrome (1) which inspired the International League of Associations for Rheumatology (ILAR) Taskforce on Classification of Childhood Arthritis to include the category of enthesitis-related arthritis (ERA) in the 1995 classification of juvenile idiopathic arthritis (JIA) (24). Two revisions of these criteria were subsequently proposed (25, 26).

Children with the SEA syndrome or with ERA are at risk of developing the other manifestations of the B27 associated disease process including axial involvement. In 1989, Burgos-Vargas and Clark reported that 75% of their Mexican patients with the SEA syndrome met the New York criteria for ankylosing spondylitis (AS) after 5 years of disease (8). These results greatly differed from ours on 13 Italian Caucasian children with SEA syndrome or with isolated HLA-B27 associated peripheral arthritis followed for more than five years in Tuscany, Central Italy (12). Only one of these patients (7.7%) developed axial involvement after five years of follow-up. Lack of evaluation of all the Mexican children at 5 years, dissimilarities in the reading of the sacroiliac plain films, the different male to female ratio together with ethnic and environmental factors were considered plausible reasons for the divergence (12). Our results were in agreement with those of other follow-up studies on Caucasian HLA-B27 positive children with peripheral arthritis and enthesitis showing a lower frequency of axial involvement (2-6).

Since 1998, a new series of children with juvenile onset uSpA (JuSpA) has been collected in the Rheumatology Department of Lucania (or Basilicata), Southern Italy, with the aim to verify the results of our previous study.

Patients and methods

Children with HLA-B27 positive ERA without any history of inflammatory spinal pain or sacroiliac joint tenderness and normal sacroiliac joints on pelvic radiographs seen for the first time at the Rheumatology Department of Lucania were entered in a special register and were followed prospectively. The Rheumatology Department of Lucania is constituted by a network of structures which includes the referral tertiary rheumatological centres of the Potenza and Matera Hospitals and 4 rheumatological outpatient clinics for the community.

We decided to take into consideration only the HLA-B27 positive patients with the aim to have a series similar to our previous one in which each enrolled child was HLA-B27 positive (12).

Each patient was examined at 6-month intervals, even if asymptomatic. Great effort was made at the first visit to convince parents of the necessity to have their children followed due to the risk of developing AS.

Special attention was paid to the peripheral and axial signs and symptoms as well as the other manifestations of the HLA-B27-associated disease process. Peripheral arthritis was defined as past or present active synovitis diagnosed by a rheumatologist and peripheral enthesitis as past or present spontaneous pain and tenderness at examination of the sites of insertion of tendons or fasciae to bone. Dactylitis was defined as diffuse swelling of the whole digit diagnosed by a rheumatologist. Cervical and lumbar pain were considered inflammatory when they lasted more than 3 months, improved with exercise, were associated with morning stiffness and aggravated by rest (23). Buttock pain was defined as pain localised to the gluteal region. It was considered alternating when it alternated between the right and the left side (23). Chest expansion, modified Shober's test, lateral spinal flexion, occiput to wall and cervical rotation were measured at each follow-up visit according to ASAS (ASsessments in Ankylosing Spondylitis) core set of measures (27). Anterior lumbar flexion was considered normal under the age of 15 if the value of the

modified Shober's test was within the normal range established by Moran *et al*. in children aged 10 to 15 (28). Acute anterior uveitis was taken into consideration only if diagnosed by an ophthalmologist. A family member was considered suffering from psoriasis if the diagnosis was convincingly made by a dermatologist.

Laboratory tests included erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) performed at baseline and every 6 months. Rheumatoid factor (RF) and antinuclear antibodies (ANA) were evaluated only at baseline.

Disease onset was defined as the day of appearance of the first manifestation of the HLA-B27 associated disease documented by a physician. Remission was defined as the absence of symptoms of axial involvement, peripheral manifestations and acute anterior uveitis in a patient with normal ESR and CRP and not taking any drugs for 3 months.

After 5 years from the inclusion, an anteroposterior view of the pelvis was obtained in all patients. The pelvic plain films were randomised and mixed with those of 14 control subjects and examined blindly and independently by two observers. The control group was formed by sex- and age-matched healthy subjects (9M, 5F) with a median age of 16.5 (range 8–21) years attending the orthopaedic department due to a mild form of scoliosis. No control had a personal or family history of SpA or psoriasis. Nobody was B27-positive or showed positive acute phase reactants.

Each sacroiliac joint was scored separately using the New York criteria (29). Films on which the observers were in disagreement were examined together and a reconciled grade was established. In patients with inflammatory spinal pain and/or buttock pain, MRI of the sacroiliac joints and the spine was performed according to the methods suggested by the ASAS group (30). Images of the sacroiliac joints were scored for bone oedema using the Leeds Scoring System which is a semiquantitative global scale (31).

The study was approved by the local ethics committee and all participants or their parents gave their informed consent.

Table I. Main demographic data and clinical features occurred during the 5-year follow-up period in the 14 patients with B27-positive JuSpA.

Pt n.	Sex	Onset age	Baseline age	Family history of SpA	Arthritis	Enthesitis	Dactylitis	Inflammatory spinal pain
1	M	9	9	psoriasis	+	-	-	-
2	F	11	11	-	-	-	+	-
3	F	3	3	psoriasis	+	+	+	-
4	M	16	16	B27+uSpA	-	+	-	buttock pain
5	M	16	16	B27+uveitis	-	+	-	-
6	F	2	3	-	+	-	-	cervical pain
7	F	10	12	B27+AS	-	+	-	-
8	M	13	16	B27+AS	+	+	+	-
9	M	5	6	psoriasis	+	-	-	-
10	M	14	14	B27+uSpA	-	+	-	-
11	M	4	16	B27+uSpA	+	+	-	-
12	F	8	9	psoriasis	+	+	-	-
13	M	13	14	B27+AS	-	+	-	-
14	M	10	12	-	+	+	-	-

AS: ankylosing spondylitis; uSpA: undifferentiated spondyloarthritis.

Results

Thirteen children, 9 boys and 4 girls, were seen in the 1998–2005 period (Table I). Of these, 4 had a first degree relative with psoriasis which was not considered an exclusion criteria for ERA as suggested by Burgos-Vargas *et al*. (32), Flatø *et al*. (18) and Stoll *et al*. (33). A rationale behind this is that juvenile onset psoriatic arthritis (PsA) does not seem to represent a defined entity (20, 21, 34, 35). According to the Vancouver criteria for juvenile PsA, which were released before the ILAR classification, two populations can be recognised: a) the first includes younger children and is very similar to ANA-positive oligoarthritis; b) the second belongs to the ERA type and represents for that reason, like adult PsA, a form of SpA (35). Our patients with a family history of psoriasis belong to the second group.

In the study period, an HLA-B27 positive child with isolated dactylitis and without any family or personal history of psoriasis was seen (Table I, Pt n. 2). This patient was included in the study also if not meeting criteria for ERA. Although dactylitis is more frequent in PsA, it may be observed in the other form of SpA including the undifferentiated ones (36). Sometimes dactylitis can be the only clinical manifestation of the HLA-B27 associated disease process (7). In view of the exceptional aspect, the case of this last patient has already been published (17).

Of the 14 patients, 3 (Pt n. 4, 7 and 13) were brought by their relatives affected by adult onset SpA, 2 (Pt n. 3 and 9) were referred with the diagnosis of SpA and the remaining 9 were seen in the community outpatient clinic. All patients with the exception of Pt n. 2, 6 and 14 had a positive family history of SpA or related diseases. Patients n. 1, 3, 9 and 12 had a first-degree relative with psoriasis. The median age of the 14 children at the onset of the disease and at our first examination were 10.0 (range 2–16) and 12.0 years (range 3–16), respectively. The parents of patient n. 3 referred that their daughter had had an episode of gastroenteritis in the months preceding the onset of her disease. All patients had negative tests for ANA and RF.

During the overall disease course, peripheral arthritis was seen in 8 patients and was the only clinical manifestation of the HLA-B27 associate disease only in 2 patients (n. 1 and 9). It was oligoarticular and asymmetric with a predominant involvement of the lower limbs. In no case were erosions seen on radiographs.

Peripheral enthesitis was seen in 10 patients of whom 4 (n. 5, 7, 10 and 13) had an isolated involvement. The heel insertions of the plantar fascia and of the Achilles tendon and the inser-

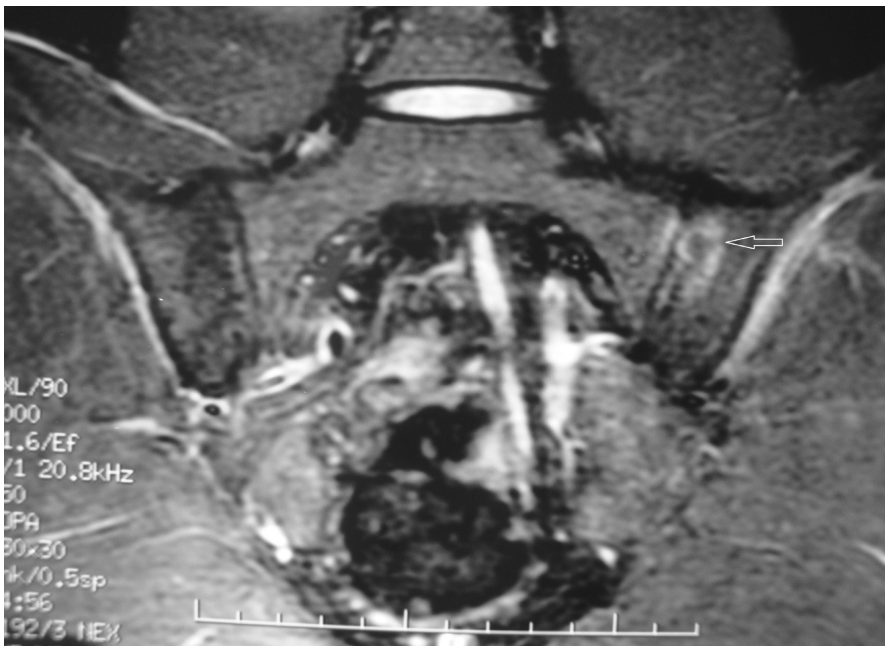

Fig. 1. STIR MRI of patient n. 4 showing bone oedema at the left sacroiliac joint (arrow).

tion of the quadriceps tendon and the patellar tendon on the patella and the tibial tubercle were the most frequently involved entheses. In patients with patellar and tibial tubercle enthesitis, the diagnosis of traction apophysitis, Osgood-Schlatter and Sinding-Larsen-Johansson diseases, was excluded (37). Patient n. 2 has had dactylitis as the only clinical manifestation of the disease since the disease onset. Two more patients (n. 3 and 8) developed dactylitis during the course of their disease. Patients n. 12 and 14 showed tenosynovitis of the lower limbs (data not shown in Table I).

Only 2 patients (n. 4 and 6) developed symptoms of axial involvement. Patient n. 6 had an episode of cervical pain when she was only 3 years old before the first examination in our outpatient clinic. Patient n. 4 had episodes of alternate buttock pain during the first years of his disease. MRI of the sacroiliac joints revealed moderate bone oedema at both joints permitting us to identify the non-radiographic phase of AS (38, 39). Figure 1 shows the involvement of the left side. He had no other episodes of buttock pain or spinal pain in the following years.

No patient showed symptoms and signs of reactive arthritis, psoriasis or inflammatory bowel disease during follow-up. Patient n. 9 had four episodes of acute anterior uveitis.

The course of the disease was self-limiting in all patients but 3 (n. 3, 5 and 12). In these 3 patients a long-lasting remission was obtained with anti-tumor necrosis factor α (TNF-α) therapy. Patient n. 5 had refractory isolated heel enthesitis and was successfully treated with adalimumab (40, 41). Patients n. 3 and 12 received etanercept for 28 and 26 months, respectively.

Sacroiliac joint x-rays were obtained at the 5-year evaluation in each enrolled patient. At the time of radiographic examination, no patient showed reduced spinal movements. Signs of sacroiliitis were found in none of the 14 patients and 14 controls. At same evaluation, we decided to obtain a new MRI in patient n. 4 which surprisingly showed no sign of acute or chronic inflammation (Fig. 2).

Discussion

The results of the present study confirm those of our previous one (12) showing a lower frequency of axial involvement after a 5-year follow-up in Italian Caucasian B27-positive JuSpA starting with peripheral manifestations. The main difference from our previous study was on the different inclusion criteria. Patients in the previous study met the Rosenberg and Petty criteria for the SEA syndrome (1) and those of the present study the ILAR criteria for ERA (26). These criteria differ in some aspects (21). However, the inclusion of only the B27 positive patients and of those with a family history of psoriasis in the second study permitted us to deal with similar populations of patients.

Similarly to our previous prospective study (12), the present was built and performed adequately. Presuming that patients with a self-limiting disease may be lost to follow-up more often than those with a persistent disease, it is necessary for all children entering into a prospective study to be examined at regular intervals without any loss. No patient in this study has been lost to follow-up. As regards to the detection of axial involvement, sacroiliac pelvic x-rays were obtained in all patients after five years since axial involvement may have an asymptomatic evolution. To reduce the observer error in the reading of sacroiliac joint radiographs, which is higher in adolescents due to normally wider joint space and indistinct subchondral margins, we evaluated pelvic plain films blindly after mixing them with those of healthy controls. In addition, we decided to perform MRI of the sacroiliac joints in patients with inflammatory low back pain and/or buttock pain since this examination can show sacroiliac joint involvement a long time before the bone abnormalities typical of sacroiliitis can be detected on the anteroposterior plain films of the pelvis (38, 39). We obtained MRI scans of the sacroiliac joints in the only patient developing symptoms of axial involvement during follow-up and we observed the typical bone oedema of sacroiliitis. We presumed to find signs of sacroiliitis on pelvic x-rays of this patient after five years of follow-up but we were surprised by the normal aspect of the joints. Then, we obtained a new MRI of this patient and, more surprisingly, we found normal aspects suggesting that sacroiliac joint involvement may occasionally have a self-limiting evolution. Some studies performed in the last few years demonstrated that not all the B27 positive patients with low back inflammatory spinal pain and bone oedema on

MRI of the sacroiliac joints develop AS in the long-term (31, 42).

When we published our paper in 1992, only a prospective follow-up study had been previously published. This article on Mexican children with SEA reported that 75% of the included patients met the New York criteria for AS after 5 years of disease (8). Since then, other follow-up studies have been made. In late 1992, Cabral and co-workers published the clinical and radiological outcome of 36 of the 39 children originally described with SEA syndrome (13). Of the 26 patients reported as having no definite SpA at the beginning of follow-up, 6 (26%) developed definite AS 10 years later. Some of these had clinical remission as long as 6 years before progression to the definite diagnosis. Therefore, it is possible that some our patients could develop axial involvement in the next few years. Selvaag *et al*. followed 12 patients with juvenile SpA for 3 years (43). However, these 12 patients had poorer health outcomes than patients with early juvenile rheumatoid arthritis. The results of this study are biased by the inclusion of more severe forms of JuSpA. In 2002, Minden and co-workers described the long-term outcome of 34 German patients with ERA (22 of the referral-based cohort and 12 of the population-based cohort of 260 patients with JIA) after a 16.5 year median follow-up duration (16). Of these, 39% had definite AS and 36% possible AS at follow-up. However, no data were given on symptoms at the first visit, on the HLA-typing and on the method used for the evaluation of the sacroiliac joint radiographs. In addition, about 17% of patients, mainly with milder disease, were lost at follow-up.

More recently, Flatø and co-workers assessed the clinical and radiographic outcome of 55 Norwegian patients with ERA after a 15-year follow-up (18). The frequency of sacroiliitis was 35% similar to that of the Minden *et al*. study (16). Limitations of this study were the retrospective application of the ILAR classification criteria and the retrospective assessment of variables from the disease onset which made its results not totally comparable with ours. Our study, although on a limited number of patients, is the only published prospective study designed with the purpose of studying the frequency of axial involvement during the course of the disease in patients with HLA-B27 positive ERA without axial involvement at the first evaluation. In addition, our patients are different from those of the Norwegian study. The patients in the Flatø *et al*. were selected from a referral centre and probably had a more severe disease in comparison with patients recruited from the general population (18). Only 3 of our 14 patients were referred to us by paediatric rheumatologists. The remaining 11 were recruited in the community outpatient clinic, where all kinds of rheumatic patients are evaluated, or were relatives of our adult patients with SpA. The confirmation of the milder disease of our patients is also suggested by the higher frequency of clinical remission during follow-up compared to the Flatø *et al*. study (18).

In a recent retrospective study on 103 Croatian patients with juvenile onset SpA according to the ESSG criteria, 82

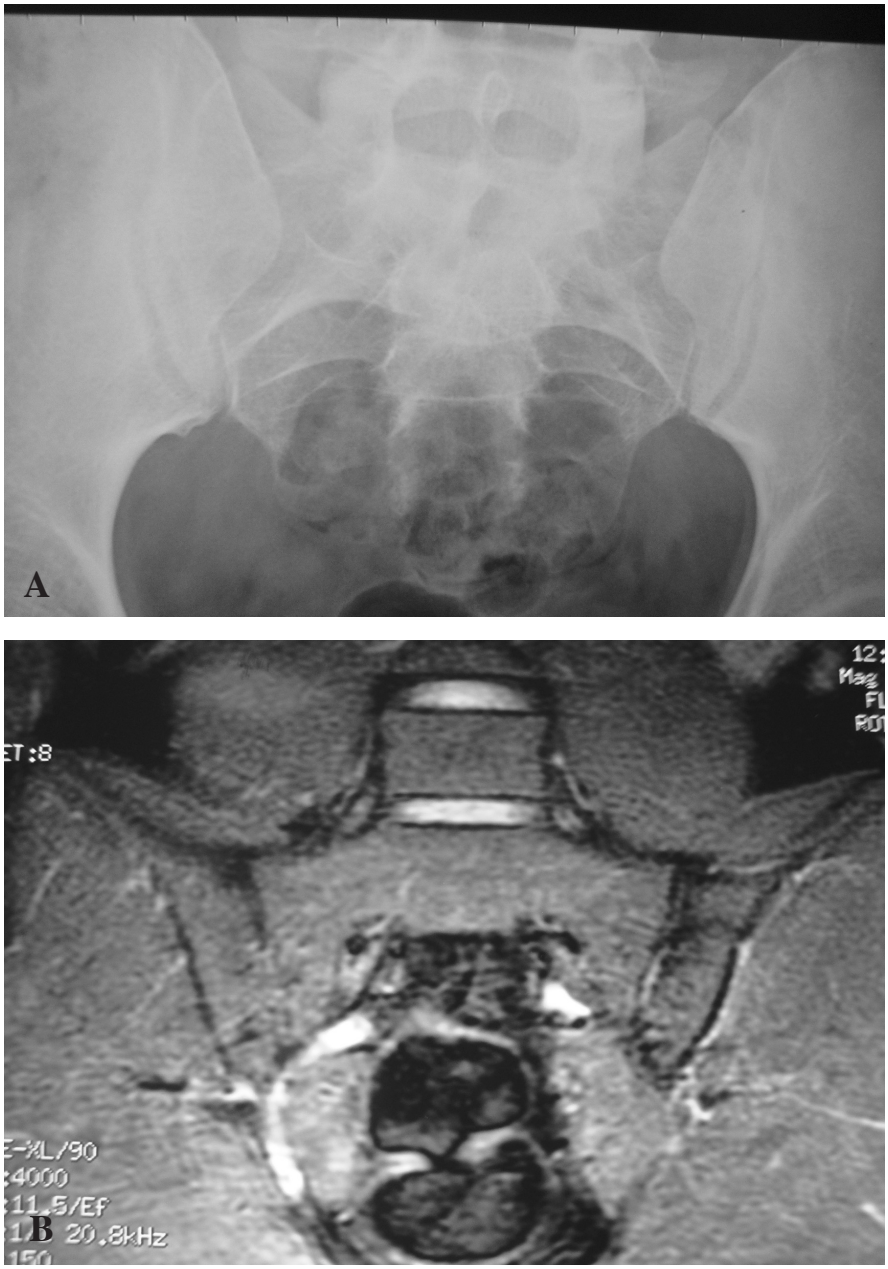

Fig. 2. Images of patient n. 4 obtained at the 5th year evaluation. **A)** Antero-posterior view of the pelvis showing normal sacroiliac joints. **B)** STIR MRI showing the disappearance of the bone oedema.

were considered suffering from JuSpA (19). Of these, 35 (42.7%) had axial symptoms at the first evaluation and all at the last visit after a mean follow-up of 6.45 years. All 82 patients had sacroiliitis of an inferior grade to that required for the diagnosis of AS according to the New York criteria at the last evaluation. However, pelvic radiographs were not read blindly to reduce observer error.

In a more recent retrospective study on 59 children with ERA followed for a mean period of 3 years in a tertiary paediatric rheumatological centre, roughly 30% developed clinical and MRI evidence of sacroiliitis. Thirty-nine (66.1%) out of the 59 were HLA-B27 positive (44).

Recent studies comparing juvenile-onset *versus* adult-onset AS showed that patients with juvenile forms had less severe axial symptoms and radiographic involvement and a better functional outcome (45, 46). These studies also support the view that the juvenile onset of SpA, at least in Caucasian subjects, is not a risk factor for a severe disease course.

Our study has some limitations. The first is the use of MRI for an early diagnosis of axial SpA only in patients with symptoms of axial involvement. Recently, Stoll and co-workers have demonstrated that sacroiliitis can be present on MRI also in the absence of suggestive symptoms or physical examination findings (33). The second limitation is given by the inclusion of only HLA-B27 positive children. As addressed before, this was made with the intention to compare patients of this study with those of the previous one (12). In this respect, the results of our two studies go beyond expectations since HLA-B27 was found to be an important predictive factor for a more extended disease in boys of an older age at onset of JIA (47). Another point that should be stressed is that 3 patients were treated with anti-TNF-α agents that could have prevented the onset of axial involvement.

In conclusion, our prospective study suggests that the onset of axial involvement in Italian Caucasian HLA-B27 positive children with ERA is rare in the first five years of disease confirming our previous results on children classified as suffering from HLA-B27 positive SEA syndrome. We want to continue to follow up these patients to see if any will develop axial symptoms and imaging evidence of axial involvement in the long term.

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