
Juvenile idiopathic arthritis.

Subgroup characteristics and comparisons between rheumatoid arthritis-like subgroups and ankylosing spondylitis-like subgroups

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ABSTRACT

In terms of adult-onset definitions, rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are rarely diagnosed in children. Adult RA is in most aspects similar to seropositive polyarticular arthritis in children, but AS differs in its clinical presentation according to age at onset. In general, the nomenclature and classifications of arthritis in children encompass subgroups with specific signs or laboratory tests and pathogenic mechanisms that distinguish one clinical form from the other. While one of these subgroups corresponds to RA, the one related to AS usually includes children with undifferentiated SpA and not definite AS. Thus, comparisons of RA and AS in children actually correspond to comparisons of various forms of childhood arthritis, currently classified as juvenile idiopathic arthritis (JIA) and AS in its early undifferentiated form. In this paper, we review these to finally compare the two populations.

Introduction

Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are today well defined diseases in adults in which differences spans from pathogenic factors to clinical features and treatment. It is difficult to determine how and when it happens, but throughout the 50s, the overlapping between RA and AS was considered so important that a number and a variety of papers used the term “rheumatoid spondylitis” when referring to AS (1-6). Of note, RA and AS had been already described long time before the 1950’s decade. Perhaps, it was until Verna Wrights writings that a definitive separation of RA and AS (or seronegative polyarthritis/spondyloarthritis) occurred (7, 8).

The issue is far more complex in children. The historic descriptions of Diamant-Berger and Still’s at the end of the 1800s recognized several clinical forms of arthritis in children, including “RA-like arthritis”, but none referred to AS (9). Diverse terms and definitions of arthritis in children appeared during the following years, but the terms and classifications most widely used were Still’s disease (10) and juvenile rheumatoid arthritis (JRA) (11). In none of these classifications RA-like or AS-like descriptions were included, but it was certainly known that some patients might have rheumatoid factor (RF) positive and adult-RA-like polyarthritis and sacroiliitis of the AS type and oligoarthritis. In fact, AS was part of exclusion criteria and “rheumatoid” was later considered a bad descriptive term since most children did not have RA-like disease. In 1976, Ansell and Wood published the remarkable classification of what they called juvenile chronic polyarthritis in which RA and AS appeared as “adult-type RA (with IgM RF [RF])” and “polyarthritis with AS type sacroiliitis” at the top of the list (Table I) (12). Interestingly, psoriatic arthritis (PsA) and intestinal bowel disease (IBD) arthritis were separated from the three subtypes of Still’s disease.

The approach of this review is therefore not an easy task, juvenile-onset RA and juvenile-onset AS correspond at some extent to two subgroups of children with arthritis named “polyarthritis, seropositive” and “enthesitis related arthritis” since the introduction of the “juvenile idiopathic arthritis” (JIA) classification (13, 14). In the first part, we will present the clinical features that distinguish each JIA subgroup. In the second part, we will present data comparing JIA or JRA and AS.

Competing interests: none declared.

Table I. Classification of juvenile chronic polyarthritis (Ansell and Wood, 1976 [ref. 12]).

1. Adult-type rheumatoid arthritis (with IgM RF)
2. Polyarthritis with ankylosing spondylitis type sacroiliitis
3. Still's disease (includes three variants) with:
 - a. Systemic manifestations
 - b. Polyarticular disease
 - c. Pauciarticular with or without chronic iridocyclitis
4. Psoriatic arthropathy (as in adults)
5. Arthritis associated with ulcerative colitis or regional enteritis (as in adults)
6. Polyarthropathies associated with other disorders such as systemic lupus erythematosus, familial Mediterranean fever, etc.

An overview of juvenile idiopathic arthritis

JIA as defined by the American College of Rheumatology (ACR) international task force and the International League of Associations for Rheumatology in 2004 is the most common inflammatory disease in childhood and can lead to severe disability (13, 15). The term JIA encompasses a group of clinically heterogeneous diseases of unknown origin, persisting for more than 6 weeks with a start before the age of 16 years. The classification has meanwhile been adapted and now has substituted the former concept and term JRA. The incidence of JIA in Caucasian populations has been estimated in between 10

and 20/100.000 children under the age of 16 years, but varies widely in other populations (16). According to the number of affected joints and extrarticular manifestations 6 months after the onset of the disease the patients are differentiated into several subgroups (Table II).

Clinical evidence indicates that neither all JIA subgroups correspond to RA nor juvenile-onset AS resemble its adult counterpart. Thus, RA versus AS comparison in children should be carefully interpreted because it totally different from the comparison of adults with those diseases.

Juvenile idiopathic arthritis comparison with adult-onset rheumatoid arthritis

Patients with JIA in the majority do not fulfill the 1987 criteria for RA (17). Even polyarticular JIA does not clearly resemble RA. Morning stiffness is common also in JIA patients, however, this is not a criterion for diagnosis of JIA. In polyarticular JIA at least 5 joints have to be affected. There is no restriction to joint regions, every joint counts, even the temporomandibular joints. Involvement of wrist, hand- and finger joints is not obligatory and the arthritis does not have to be symmetric, which off course is present in most polyarticular JIA patients. Rheumatoid nodules are rarely

found. Test for RF are necessary for sub-classification (seropositive polyarticular JIA). They however have to be positive on at least 2 occasions at least 3 months apart. If they were present in a patient with only 3 joints affected, this patient could be unclassifiable. Finally, there is no need for radiographic studies for JIA diagnosis.

In summary, JIA as a whole group differs markedly from RA. Furthermore, also patients with polyarticular JIA at the beginning of the disease may not fulfill the ACR criteria for RA. Classification as JIA according to the ILAR-criteria (14) enables early diagnosis and initiation of treatment.

Juvenile-onset and adult-onset AS comparison

Juvenile and adult onset SpA, particularly AS differ in some aspects, but in general, the evidence does not support that they correspond to different diseases. Most differences consist in symptoms at onset (18-25). In contrast to adults, children and adolescents with AS have peripheral arthritis and enthesitis in the initial years and axial symptoms five to ten years later. The severity of AS, excepting the spine, is greater in juveniles than in adults since more juveniles require hip replacements, more are in functional classes III and IV, and their mean Bath AS functional index scores

Table II. Subclassification of juvenile idiopathic arthritis (JIA) (Petty, *et al.* 1998 [ref. 13], Petty, *et al.* 2004 [ref. 14]).

Subtypes of JIA	Main extrarticular manifestations	Exclusion criteria	Frequency ^s
1 Systemic arthritis	Fever, rash, hepatosplenomegaly, pericarditis, pleuritis, lymphadenopathy, vasculitis, growth impairment, dystrophy	a, b, c, d	6%
2 Seronegative polyarthritis*	Tenosynovitis, uveitis, vasculitis	a, b, c, d, e	15%
3 Seropositive polyarthritis*	Tenosynovitis, rheumatoid nodules, vasculitis, Sjögren's syndrome	a, b, c, e	2%
4a Persistent oligoarthritis**	Chronic uveitis	a, b, c, d, e	46%
4b Extended oligoarthritis***			7%
5 Enthesitis related-arthritis	Enthesitis, acute uveitis	a, d, e	14%
6 Psoriasis and arthritis	Psoriasis, uveitis	b, c	8%
7 Not classifiable or fitting into several groups (1-6)		Various	3%

Specific exclusion criteria: **a:** psoriasis or psoriasis in a first grade relative; **b:** presence of HLA-B27, male gender and age above 6 years; **c:** ankylosing spondylitis, enthesitis-associated arthritis, sacroiliitis accompanied by chronic inflammatory bowel disease, Reiter's disease in a first grade relative; **d:** Presence of RFs in at least 2 occasions at least 3 months apart; **e:** systemic manifestations.

* At least 5 joints were involved during the first 6 months of the disease; ** A maximum of 4 joints were involved during the first 6 months of the disease;

*** A maximum of 4 joints were involved during the first 6 months of the disease. Thereafter at least 5 joints were involved.; ^sFrequency according to the German Core Dokumentation 2006 on 4116 patients (Minden, 2009).

are higher. Norwegian and Mexican children with SpA show stronger associations with HLA-DRB1*08, HLA-DPB1*0301, and LMP2 gene polymorphism (26-29).

Systemic onset juvenile idiopathic arthritis

Patients met the definition of systemic onset JIA (SoJIA) if arthritis is present or follows daily fever of at least 2 weeks duration, that is documented to be quotidian for at least 3 days, and accompanied by one or more of the following: 1) evanescent, non-fixed, erythematous rash, 2) generalized lymph node enlargement, 3) hepatomegaly or splenomegaly, or 4) serositis. The fever usually rapidly arises once per day, most commonly in the afternoon or evening. Infectious and malignant diseases have to be excluded carefully by appropriate investigations. Serum levels of C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) are highly elevated accompanied by a pronounced leukocytosis and thrombocytosis. There is normocytic anemia at onset and then microcytic anemia afterwards. RF and ANA test will remain negative indicating a rather autoinflammatory than autoimmune pathogenesis. In the Caucasian population, SoJIA accounts for up to 10% of all JIA cases with no gender predominance while in Japanese it is the most frequent subtype of JIA. Patients with SoJIA tend to respond poorly to methotrexate and etanercept (29, 30) while targeting interleukin-1 using anakinra or rilonacept or interleukin-6 using tocilizumab is promising (31-33). Due to both, their poor response to treatment and to the high inflammatory state characterized by elevated acute phase response growth impairment is frequent and the patients are at risk for the development of severe destructive joint disease, severe organ involvement, amyloidosis and macrophage activation syndrome. Uveitis however, rarely is present in SoJIA patients but should prompt to rule out an infectious origin as well as a hereditary episodic fever syndrome especially Muckle-Wells syndrome and neonatal-onset multi-systemic inflammatory disease (NOMID).

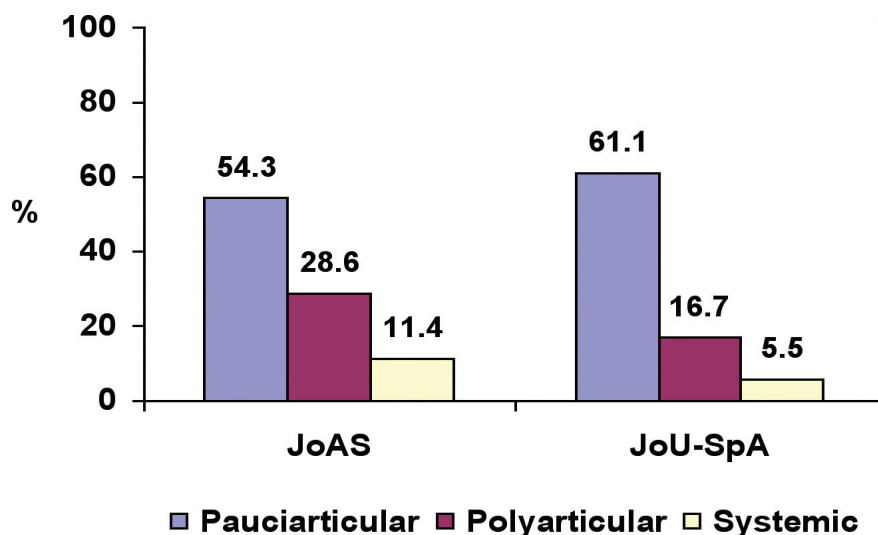


Fig. 1. Patients with juvenile-onset AS and juvenile-undifferentiated SpA that fulfilled JRA diagnostic criteria 6 months after onset (ref. 35).

There is an equivalent to SoJIA with onset in adulthood: adult onset Still's disease (AoSD), which is a relatively rare inflammatory disease with daily spiking fever, arthritis or joint pain accompanied by a salmon-pink rash. It can progress into chronic arthritis and resembles SoJIA sharing its complications, joint destruction, organ involvement and especially macrophage activation syndrome. Lung and heart inflammation occur more rarely. RF and antinuclear antibodies (ANA) tests will be negative as well. Diagnosis is made according to Yamaguchi's criteria (34): Major criteria, (1) fever $>39^{\circ}\text{C}$ for at least 1 week, (2) arthralgia/arthritis for at least 2 weeks, 3) a typical rash, 4) leukocytosis of at least $10,000/\mu\text{l}$ with at least 80% polymorphonuclear cells; minor criteria, 1) sore throat, 2) lymphadenopathy 3) increased liver function tests and 4) the absence of RF and ANA. Five or more criteria, of which at least 2 are major criteria, yield 96% sensitivity and 92% specificity.

Up to 11% of patients with juvenile-onset AS and 6% of those with juvenile-onset undifferentiated SpA may fulfil SoJIA criteria since they may have fever, lymph node enlargement, leukocytosis, and thrombocytosis in the initial six months of disease or later on during active periods of the disease (Fig. 1) (35). Differential diagnosis in these cases may rely on the presence of enthesopathy or HLA-B27.

Seronegative polyarthritis

A polyarticular disease is defined as the presence of arthritis for at least 6 weeks affecting 5 or more joints during the first 6 months of disease. Tests for RF have to be negative in a least 2 occasions at least 3 months apart. ANA are present in 43%. Of importance, numerous patients have normal ESR and CRP levels. This subgroup accounts for 10-15% of all JIA cases. The number of girl exceeds the number of boys by the factor of 3 (36). The arthritis typically is symmetric and affects small and large joints involving also the upper extremities and the wrists. The cervical spine and temporomandibular joints are frequently affected. Up to 10% of patients suffer from chronic uveitis. Patients frequently show growth delay which at the end can lead to short stature but also regional growth is often affected leading to micrognathia (growth of the mandibles), short wrists (premature closure of growing plates and loss of height of the wrists), short fingers (affection of the growing plates) as well as short deformed feet. Children of all ages may be affected with a peak incidence in the pre-school age. Rarely the diseases onset occurs in the first year of life. Exclusions are 1) RF, 2) features of systemic arthritis, 3) psoriasis, 4) HLA B27 in a boy of at least 6 years and a first grade relative with a SpA. Nearly 30% of the patients with juvenile-onset AS and 17% of those with

juvenile-onset undifferentiated SpA fulfill the former seronegative polyarticular JRA criteria and surely many more the seronegative polyarthritis JIA criteria since most patients with AS and undifferentiated SpA develops polyarthritis throughout the course of the disease (35). The differentiation of these groups basically depends on the JIA exclusion criteria (14).

Seropositive polyarthritis

Seropositive polyarticular JIA is the only JIA subgroup resembling adult RA; in previous classifications it was called juvenile RA (12) or seropositive polyarticular JRA (11). It is defined as arthritis affecting 5 or more joints during first 6 months of disease, associated with a positive RF test in two occasions at least 3 months apart. Joint involvement is symmetrical with small and large joints affected. Rheumatoid nodules can be found. Teenage children are more frequently affected and girls account for 87% of patients. ANA may be present but chronic uveitis does not occur. The immunogenetic profile is similar to adult RA, specifically association with HLA-DR4 allele. Likewise, systemic manifestations including elevated ESR and CRP. Compared to the other JIA subtypes prognosis is poor and remission occurs rarely (36). Beside the clinical manifestations of adult RA, onset of the disease before adulthood brings along affection of growth. Since the disease usually starts after puberty adult height may be normal. Localized growth however can be affected. The growth of the distal ulna is disturbed leading to typical wrist scoliosis with an ulnar deviation at the wrists and a radial deviation of the fingers which is the opposite to the classical ulnar deviation of the finger joints in patients with adult rheumatoid arthritis. Affection of the finger joints lead to growth disturbance of single finger bones with prolongation or shortening of fingers. Furthermore, the involvement of the feet leads to shortened feet. Involvement of the temporomandibular joints leads to micrognathia.

The radiographic aspects of this form of arthritis frequently include joint space narrowing, erosions of the articular

surface, subchondral cysts, and ankylosis of some small joints.

By definition, the presence of RF makes the differentiation of this JIA subgroup from AS and undifferentiated juvenile onset diseases (see below). Nevertheless, some patients with juvenile-onset AS or undifferentiated SpA would eventually have RF throughout the course of the disease.

Persistent and extended oligoarthritis

Oligoarthritis is defined as arthritis affecting 1 to 4 joints during the first 6 months of disease. In persistent oligoarthritis the disease affects no more than 4 joints throughout the disease course while extended oligoarthritis involves 5 joints or more after the first 6 months of disease. In Caucasians, this subgroup accounts for more than 50% of all JIA cases. It frequently affects pre school girls and can also occur in the first year of life. Patients are excluded from this subgroup if there is (1) a family history of psoriasis confirmed by dermatologist in first or second degree relative(s), (2) a family history consistent with medically confirmed HLA-B27 associated disease in at least one first or second degree relative, (3) a positive RF test, or (4) in HLA-B27 positive male with onset of arthritis after age of 6 and (5) in the presence of systemic arthritis with fever and a typical rash.

Joint disease is usually limited and frequently remits, particularly in persistent oligoarthritis. More than half of the patients have no more active joint disease in adulthood (36). However, asymptomatic anterior uveitis occurs in about 20% of patients. This complication may lead to damage of one or both eyes with cataracts, glaucoma, retinopathy, and ultimately visual impairment. Upon regularly follow up and appropriate treatment, blindness can be prevented. Since most patients with juvenile-onset AS have oligoarthritis in the initial six months of disease, differential diagnosis with this subgroup of JIA is certainly difficult. Age at onset, sex distribution, ANA, HLA-B27, and the type of eye involvement may help in differentiating oligoarthritis JIA from juvenile-onset AS.

Psoriasis and arthritis

This subtype is defined as the presence of arthritis and psoriasis, or arthritis and at least 2 of the following: 1) dactylitis, 2) nail abnormalities (pitting or onycholysis), 3) a minimum of 2 pits one or more nails, 4) family history of psoriasis in at least one 1st degree relative. Exclusions are RF or systemic arthritis. Half the patients do not have psoriasis at onset. The disease may affect large and small joint and may progress from oligoarticular disease to polyarthritis. All joints including distal interphalangeal joints may be affected. The pattern may be asymmetric, a radial pattern may be found as well. Children of all ages may be affected including those of the first year of life.

Two major subgroups of patients with juvenile-onset PsA may be recognized (37-39). One occurs at early age and presents with oligo- and polyarthritis. The other occurs in HLA-B27 positive boys or girls at an older age; the clinical picture includes lower limb oligoarthritis, enthesopathy and axial involvement. Thus, PsA includes a subgroup of patients with SpA in whom AS may be recognized some years after onset. Probable, the clinical features of juvenile-onset psoriatic SpA do not differ from juvenile-onset AS, but there are no studies comparing such subgroups of patients. In contrast, peripheral disease may affect the upper limb joints, including the small joints of the hands in more patients with psoriatic SpA than in juvenile-onset AS.

Enthesitis-related arthritis

This subtype is defined as the presence of arthritis and enthesitis or arthritis or enthesitis with at least 2 of, 1) sacroiliac joint tenderness and/or inflammatory spinal pain, 2) pain in spine at rest with morning stiffness in the spine, 3) presence of HLA-B27, 4) a family history in at least one 1st or 2nd degree relative of medically confirmed HLA-B27 associated disease (AS, IBD, acute [symptomatic] anterior uveitis), 5) anterior uveitis that is usually associated with pain, redness or photophobia, 6) onset of arthritis in a boy after age 8. The presence of psoriasis confirmed by dermatologist in at least one 1st or 2nd

degree relative or the presence of signs of systemic arthritis are excluded.

Enthesitis related arthritis corresponds to some, but not all spondyloarthropathies (SpA) (40). Undifferentiated SpA and AS might be included in this subgroup, but psoriatic SpA, reactive arthritis, and inflammatory bowel disease associated arthritis are excluded. Differences between this JIA subgroup and all other JIA subgroups are listed in the inclusion and exclusion criteria (Table II) (14).

Prognosis

Although the overall prognosis for most children with chronic arthritis is comparably good, about half of the patients suffer from active joint disease until adulthood (36). Ongoing disease led to progressive damage with increasing HAQ-scores. Furthermore, mortality rates are elevated up to 4 fold compared to the general population which exceeds the elevation of mortality of rheumatoid arthritis.

In at least 10% of patients the disease is refractory to conventional therapies, consisting of a combination of non-steroidal anti-inflammatory drugs, corticosteroids and disease modifying anti-rheumatic drugs with their major representative methotrexate (MTX) and necessitates the use of biologics.

The outcome of JIA is variable depending on the subgroup of JIA. In some subgroups many children experience spontaneous remission of their joint disease while in other subgroups persistent destructive arthritis frequently occur. 22–41% of patients with oligoarticular disease, about 50% of patients with polyarticular disease and 27–48% of patients with systemic onset JIA will suffer from persistently active joint disease over a period of 10 years (41). This is accompanied by an inverse rate of remissions (42).

Clinical experience suggests that more children than expected have ongoing disease in adulthood. Though the physical outcome of patients with JIA is relatively good compared to adult patients with rheumatoid arthritis, many patients still have active disease in adulthood and health status and quality of life are reduced in patients with all types of JIA (15). A large population-based survey

demonstrated active disease in approximately half of the patients with JIA with alterations in their body function and structure after disease duration of more than 15 years. One third of them had significant functional limitations and joints contractures. Fortunately, less than 10% are severely disabled or handicapped (35). In this large population remission rates differs markedly in between the JIA subgroup. While patients with oligoarticular JIA 15 years after onset of their disease showed remission in 72%, this rate was lower in systemic JIA (49%), much lower in seronegative polyarthritis (23%) and enthesitis-related arthritis (18%). Remission could not be documented in seropositive polyarthritis (35).

Regarding juvenile-onset AS, enthesitis related arthritis, or juvenile-onset SpA, the probability of remission five years after onset only reaches 17% of patients with juvenile-onset SpA (43); by 10 years of disease less than 50% are in remission (42); and by 17 years after onset more than 50% of the patients still have active disease (36). Sixty percent of the patients have moderate to severe functional limitations 10 years after onset, particularly those with disease activity for more than five years (42); however, low level disability has also been found after 27 years of disease (44). Compared with other subgroups of JIA, patients with juvenile-onset SpA have higher bodily pain and childhood health assessment questionnaire scores, poorer physical health and lower physical functioning and health related quality of life (45–47). Patients with juvenile-onset PsA had poorer health than healthy population 15 years after onset and lower SF-36 scores than other JIA subgroups by 23 years of disease (48).

Growth is altered in relation to the onset age, the subtype of JIA and the extend of systemic inflammation. Especially prepubertal patients are at risk for short stature (49). In a large population based cohort, the median height female patients was 166 cm (range 148–186 cm), which is lower than the median height (168 cm) among healthy women (50). In male patients, the median height was comparable with the average height

among men in the general population. The lowest median heights were observed in the group with systemic arthritis: 164 cm for women and 173 cm for men (36).

Much more common are localized growth disturbances, while limb length discrepancies were most pronounced if an asymmetric involvement of the knee joint is present. The affected knee will show an overgrowth which can exceed several centimetres and in average is about 1 cm. Micrognathia is frequent in those children with affected temporomandibular joints. It is due to growth impairment of the mandible and affects 22% of patients with polyarticular JIA (RF-negative), 13% with systemic JIA, 8% with oligoarticular JIA, and 6% with other subtypes of JIA.

Treatment

In approximately one third of patients, the disease is controlled with non-steroidal anti-inflammatory drugs and an appropriate program of physical and occupational therapy. The remainders are candidates for more aggressive therapy with anti-rheumatic drugs. MTX was shown to have a therapeutic advantage over placebo, with an acceptable safety profile, in a randomized, controlled trial in children with juvenile rheumatoid arthritis who had polyarticular involvement (regardless of the type of onset) (51–53). The majority of all other disease modifying anti-rheumatic drugs are either not licensed for children or have not been studied successfully in randomized controlled trials. In this situation “off-label” treatment becomes necessary.

Leflunomide has been proved to be effective in patients with active polyarticular juvenile arthritis in a double blind randomized study compared to MTX (54). However it currently is not licensed for children. Since in there are no second line agents available in oligoarticular JIA, intra-articular corticosteroids are helpful and should commonly be used and preferred compared to non-steroidal anti-inflammatory drugs (55).

Systemic corticosteroids at higher dosage are less indicated due to adverse events including disturbance of growth. Small oral prednisone (about 0.1 to

0.2 mg/kg) is used as a bridging treatment until reduction of disease activity through treatment with slow acting drugs.

Especially in patients with polyarticular and systemic subtypes MTX it is not always successful. Anti-Tumour-Necrosis-Factor- α therapy with etanercept has shown success in polyarticular JIA patients aged at least 4 years in a single randomised controlled study (56-58). Data of the German Enbrel JIA registry showed that about 80% of JIA patients were treated by combining etanercept and MTX instead of replacing MTX by etanercept (49). In adults with RA, the combination of etanercept and MTX is associated with a higher response rate (59) and it has been suggested that in JIA combination therapy of etanercept with MTX is superior to mono therapy (60).

Adalimumab has been studied as a single treatment and in combination with methotrexate and is an alternative (61). Abatacept has been studied in polyarticular JIA (62) and recently been licensed first by the Food and Drug Administration. Tocilizumab has been studied in systemic onset JIA patients in a double blind controlled randomized trial and was first licensed in Japan (33). Tocilizumab however has also been licensed in Japan for polyarticular JIA albeit only 19 polyarticular patients have been studied in an open trial. Anakinra, which has been approved for adult RA since 2001 has been studied in polyarticular and SoJIA; while in the former it did not show superiority over placebo, in SoJIA the effect was significantly superior (31, 63).

Etanercept and infliximab have been shown to induce rapid and sustained improvement of signs and symptoms of disease activity in patients with juvenile onset SpA, including enthesitis-related arthritis and AS (64-66).

Juvenile idiopathic arthritis (formerly JRA) versus juvenile-onset AS

Before the 1980s, most clinical descriptions referred to juvenile-onset AS and the diagnosis was made according to New York criteria (67). Patients were either boys or girls who have involve-

ment of the sacroiliac joints as well as the spine and less frequently of the peripheral joints.

With the advent of HLA-B27 tissue typing, people realized that there was an excess of HLA-B27 children with juvenile rheumatoid arthritis (JRA) or juvenile chronic arthritis (JCA) (68-70). Interestingly, most cases corresponded to boys around 10 years old with oligoarthritis involving the lower-limb joints. Along with these findings, the earliest follow-up of HLA-B27 JCA children reported by Edmonds *et al.* (69) indicated that most of these cases would eventually fulfil AS criteria. That study seemed to confirm a long term outcome follow up of Still's disease which found AS in an important number of patients with peripheral arthritis (71). Soon became clear that juvenile-onset AS presented in most cases as peripheral arthritis and not with spinal or sacroiliac involvement. It was also clear that most patients were diagnosed and classified within the oligoarticular subgroup of JRA or JCA.

In the early 80s, two papers described the earliest forms of SpA in children and incorporated enthesopathy as a distinctive element: the seronegative enthesopathy and arthropathy (SEA) syndrome (72) and HLA-B27 associated spondyloarthritis and enthesopathy in childhood (73).

Long term follow-ups of HLA-B27 patients with JRA or JCA showed that more than two thirds of them had actually SpA, including AS (74-76). Rheumatologists and pediatric rheumatologists recognized the need to differentiate the subgroup of patients who eventually will develop AS from other JRA/JCA subgroups, not only because of the name of their disease, but because of their outcome, and treatment. Patients with AS were mostly HLA-B27 boys older than six to eight years old with oligoarthritis and enthesopathy involving the lower limbs, negative tests for IgM RF and ANA and positive family history of SpA, but there are no studies at present comparing JRA/JCA with juvenile onset AS. Diagnostic criteria for juvenile-onset AS were proposed (77-79), but they never underwent a process of validation.

In 1995, one of us reported on clinical data allowing the differentiation of juvenile-onset AS from the systemic, type I oligoarticular, and polyarticular JRA early on in the course of the disease and on the long-term (35). At 6 months of disease, various features characterized juvenile-onset AS versus JRA: enthesopathy (82.9% vs. 0%; $p < 0.0001$, OR=321.4), tarsitis (71.4% vs. 1.3%; $p < 0.0001$, OR=185.0), oligoarthritis (54.3% vs. 30.7%; $p = 0.03$, odds ratio [OR]=2.7), and lumbar/sacroiliac symptoms (11.4% vs. 0%; $p = 0.02$, OR=11.9). At 12 months, the features found more frequently among juvenile-onset AS patients than JRA patients were enthesopathy (88.6% vs. 4.0%; $p < 0.0001$, OR=186.0), tarsitis (85.7% vs. 10.7%; $p < 0.0001$, OR=50.3), and knee disease (100.0% vs. 82.7%; $p = 0.04$, OR=8.0). Definite involvement of the spine and sacroiliitis occurred after a mean $\pm$ SD of 7.3 ± 2.0 years.

We also looked for symptoms in juvenile-onset AS that could be specific for each JRA subgroup (Fig. 1). Interestingly, patients with juvenile-onset AS may also have fever, lymph node enlargement, polyarthritis, leukocytosis, and thrombocytosis and fulfill the JRA diagnostic criteria. Thus, the differentiation between these JRA subgroups and juvenile-onset AS is much more difficult.

The differentiation of juvenile-onset AS from JIA, including the subgroups with no equivalence to adult onset RA is definitely important. Demographics and pathogenic factors differ among the different subgroups; clinical features and outcome also differ; ultimately, treatment is also different.

References

1. YOUNG JH: Rheumatoid (ankylosing) spondylitis: its early manifestations and early diagnosis. *Med J Aust* 1951; 2: 761-4.
2. CRENSHAW AH, HAMILTON JF: Rheumatoid spondylitis. *South Med J* 1952; 45: 1055-61.
3. GILMOR CS, CRAMER Q: Rheumatoid spondylitis. *Mo Med* 1954; 51: 994-6.
4. POLLEY HF: The diagnosis and treatment of rheumatoid spondylitis. *Med Clin North Am* 1955; 12: 509-28.
5. BLUMBERG B, RAGAN C: The natural history of rheumatoid spondylitis. *Bull Rheum Dis* 1955; 6: 95-6.
6. HARLEY JB: Rheumatoid spondylitis; a review of 105 cases. *W V Med J* 1956; 52: 301-4.

7. MOLL JM, HASLOCK I, MACRAE IF, WRIGHT V: Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies, and Behçet's syndrome. *Medicine* (Baltimore) 1974; 53: 343-64.
8. WRIGHT V: Seronegative polyarthritis: a unified concept. *Arthritis Rheum* 1978; 21: 619-33.
9. BYWATERS EG: The history of pediatric rheumatology. *Arthritis Rheum* 1977; 20 (2 Suppl.): 145-52.
10. ANSELL BM, BYWATERS EGL: Prognosis in Still's disease. *Bull Rheum Dis* 9: 189-92.
11. BREWER EJ JR, BASS J, BAUM J *et al.*: Current proposed revision of JRA criteria. JRA Criteria Subcommittee of the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Section of The Arthritis Foundation. *Arthritis Rheum* 1977; 20 (Suppl.): 195-9.
12. ANSELL BM, WOOD PHN: Prognosis in juvenile chronic polyarthritis. *Clin Rheum Dis* 1976; 2: 397-412.
13. PETTY RE, SOUTHWOOD TR, BAUM J *et al.*: Revision of the proposed criteria for juvenile idiopathic arthritis: Durban 1997. *J Rheumatol* 1998; 25: 1991-4.
14. PETTY RE, SOUTHWOOD TR, MANNERS P *et al.*: International League of Associations for Rheumatology: International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004; 31: 390-2.
15. RAVELLI A, MARTINI A: Juvenile idiopathic arthritis. *Lancet* 2007; 369: 767-78.
16. MANNERS PJ, BOWER C: Worldwide prevalence of juvenile arthritis why does it vary so much? *J Rheumatol* 2002; 29: 1520-30.
17. ARNETT FC, EDWORTHY SM, BLOCH DA *et al.*: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
18. MARKS S, BENNETT M, CALIN A: The natural history of juvenile ankylosing spondylitis: a case control study of juvenile and adult onset disease. *J Rheumatol* 1982; 9: 739-41.
19. GARCÍA-MORTEO O, MALDONADO-COCCO JA, SUÁREZ-ALMAZOR ME *et al.*: Ankylosing spondylitis of juvenile onset: comparison with adult onset disease. *Scand J Rheumatol* 1983; 12: 246-8.
20. CALIN A, ELSWOOD S: The natural history of juvenile onset ankylosing spondylitis: 24 year retrospective case control study. *Br J Rheumatol* 1988; 27: 91-3.
21. BURGOS-VARGAS R, NARANJO A, CASTILLO J *et al.*: Ankylosing spondylitis in the Mexican Mestizo: patterns of disease according to age at onset. *J Rheumatol* 1989; 16: 186-91.
22. BAEK HJ, SHIN KC, LEE YJ *et al.*: Juvenile onset ankylosing spondylitis (JAS) has less severe spinal disease course than adult onset ankylosing spondylitis (AAS): clinical comparison between JAS and AAS in Korea. *J Rheumatol* 2002; 29: 1780-5.
23. STONE M, WARREN RW, BRUCKEL J *et al.*: Juvenile-onset ankylosing spondylitis is associated with worse functional outcomes than adult-onset ankylosing spondylitis. *Arthritis Rheum* 2005; 53: 445-51.
24. GENSLER LS, WARD MM, REVEILLE JD *et al.*: Clinical, radiographic and functional differences between juvenile-onset and adult-onset ankylosing spondylitis: results from the PSOAS cohort. *Ann Rheum Dis* 2008; 67: 233-7.
25. O'SHEA FD, BOYLE E, RIARH R *et al.*: Comparison of clinical and radiographic severity of juvenile-onset versus adult-onset ankylosing spondylitis. *Ann Rheum Dis* 2009; 68: 1407-12.
26. PLOSKI R, FLATO B, VINJE O *et al.*: Association to HLA-DRB1*08, HLA-DPB1*0301 and homogeneity for an HLA-linked proteasome gene in juvenile ankylosing spondylitis. *Human Immunol* 1995; 44: 88-96.
27. MAKSYMOWYCH P, LUONG M, WONG C *et al.*: The LMP2 polymorphism is associated with susceptibility to acute anterior uveitis in HLA-B27 positive juvenile and adult Mexican individuals with AS. *Ann Rheum Dis* 1997; 56: 807-14.
28. MAKSYMOWYCH WP, GORODEZKY C, OLIVO A *et al.*: HLA-DRB1*09 influences the development of disease in Mexican Mestizo with spondyloarthropathy. *J Rheumatol* 1997; 24: 904-7.
29. QUARTIER P, TAUPIN P, BOURDEAUT F *et al.*: Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type. *Arthritis Rheum* 2003; 48: 1093-101.
30. HORNEFF G, SCHMELING H, BIEDERMANN T *et al.*: The German etanercept registry for treatment of juvenile idiopathic arthritis. *Ann Rheum Dis* 2004; 63: 1638-44.
31. QUARTIER P, ALLANTAZ F, CIMAZ R *et al.*: Anakinra in systemic onset juvenile idiopathic arthritis: result of a multicenter double-blind trial (ANAJIS). *Ann Rheum Dis* 2008; 68 Supplement.
32. LOVELL DJ, GIANINNI EH, KIMURA Y *et al.*: Preliminary evidence for bioactivity of IL-1 trap (Rilonacept), a long acting il-1 inhibitor, in systemic juvenile idiopathic arthritis (sJIA). *Arthritis Rheum* 2006; 54: S325.
33. YOKOTA S, IMAGAWA T, MORI M *et al.*: Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. *Lancet* 2008; 371: 998-1006.
34. YAMAGUCHI M, OHTA A, TSUNEMATSU T *et al.*: Preliminary criteria for classification of adult Still's disease. *J Rheumatol* 1992; 19: 424.
35. BURGOS-VARGAS R, VÁZQUEZ-MELLADO J: The early clinical recognition of juvenile-onset ankylosing spondylitis and its differentiation from juvenile rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 835-44.
36. MINDEN K, NIEWERTH M, LISTING J *et al.*: Long-term outcome in patients with juvenile idiopathic arthritis. *Arthritis Rheum* 2002; 46: 2392-401.
37. SOUTHWOOD TR, PETTY RE, MALLESON PN *et al.*: Psoriatic arthritis in children. *Arthritis Rheum* 1989; 32: 1014-21.
38. STOLL ML, ZURAKOWSKI D, NIGROVIC LE *et al.*: Patients with juvenile psoriatic arthritis comprise two distinct populations. *Arthritis Rheum* 2006; 54: 3564-72.
39. HAMILTON ML, GLADMAN DD, SHORE A *et al.*: Juvenile psoriatic arthritis and HLA antigens. *Ann Rheum Dis* 1990; 49: 694-7.
40. BURGOS-VARGAS R, RUDWALEIT M, SIEPER J: The place of juvenile onset spondyloarthropathies in the Durban 1997 ILAR classification criteria of juvenile idiopathic arthritis. *J Rheumatol* 2002; 29: 869-74.
41. PETTY RE: Prognosis in children with rheumatic diseases: justification for consideration of new therapies. *Rheumatology* 1999; 38: 739-42.
42. FLATØ B, AASLAND A, VINJE O, FØRRE O: Outcome and predictive factors in juvenile rheumatoid arthritis and juvenile spondyloarthropathy. *J Rheumatol* 1998; 25: 366-75.
43. MINDEN K, KIESSLING U, LISTING J *et al.*: Prognosis of patients with juvenile chronic arthritis and juvenile spondyloarthropathy. *J Rheumatol* 2000; 27: 2256-63.
44. PACKHAM JC, HALL MA: Long-term follow-up of 246 adults with juvenile idiopathic arthritis: functional outcome. *Rheumatology* (Oxford) 2002; 41: 1428-35.
45. SELVAAG AM, FLATØ B, DALE K *et al.*: Radiographic and clinical outcome in early juvenile rheumatoid arthritis and juvenile spondyloarthropathy: a 3-year prospective study. *J Rheumatol* 2006; 33: 1382-91.
46. FLATØ B, HOFFMANN-VOLD AM, REIFF A *et al.*: Long-term outcome and prognostic factors in enthesitis-related arthritis: a case-control study. *Arthritis Rheum* 2006; 54: 3573-82.
47. DUARTE-SALAZAR C, GUZMÁN-VÁZQUEZ S, SOTO-MOLINA H *et al.*: Disability impact on quality of life in Mexican adults with juvenile idiopathic arthritis and juvenile ankylosing spondylitis. *Clin Exp Rheumatol* 2007; 25: 922-7.
48. FLATØ B, LIEN G, SMERDEL-RAMOYA A *et al.*: Juvenile psoriatic arthritis: longterm outcome and differentiation from other subtypes of juvenile idiopathic arthritis. *J Rheumatol* 2009; 36: 642-50.
49. HORNEFF G, FÖLDVARI I, GANSER G *et al.*: Growth reconstitution in juvenile idiopathic arthritis upon treatment with Etanercept. *ACR* 2007, Boston, *Arthritis Rheum* 2007; 56 (Suppl.): S375-376.
50. HESSE V: Wachstum und Reifung [Growth and development]. In: MENG W, ZIEGLER R, (Eds.) *Endokrinologie: Grundlagen, Klinik und Praxis* [Endocrinology: bases, clinic and practice]. Ulm: Gustav Fischer Verlag.
51. GIANNINI EH, BREWER EJ, KUZMINAN *et al.*: Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. *N Engl J Med* 1992; 326: 1043-9.
52. RUPERTO N, MURRAY KJ, GERLONI V *et al.*: A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. *Arthritis Rheum* 2004; 50: 2191-201.
53. WOO P, SOUTHWOOD TR, PRIEUR AM *et al.*: Randomized, placebo-controlled, crossover trial of low-dose oral methotrexate in children

- with extended oligoarticular or systemic arthritis. *Arthritis Rheum* 2005; 43: 1849-57.
54. SILVERMAN E, MOUY R, SPIEGEL L *et al.*: Leflunomide in Juvenile Rheumatoid Arthritis (JRA) Investigator Group. Leflunomide or methotrexate for juvenile rheumatoid arthritis. *N Engl J Med* 2005; 352: 1655-66.
55. BEUKELMAN T, GUEVARA JP, ALBERT DA: Outcome in the initial treatment of knee monoarthritis in JIA: Results of a decision analysis model. *Arthritis Rheum* 2007; 54 (Suppl.).
56. LOVELL DJ, GIANNINI EH, REIFF A *et al.*: Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *N Engl J Med* 2000; 342: 763-9.
57. LOVELL DJ, REIFF A, ILOWITE NT *et al.*: Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. *Arthritis Rheum* 2008; 58: 1496-504.
58. LOVELL DJ, REIFF A, JONES OY *et al.*: Long-term safety and efficacy of etanercept in children with polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum* 2006; 54: 1987-94.
59. KLARESKOG L, VAN DER HEIJDE D, DE JAGER JP *et al.*: Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004; 363: 675-81.
60. HORNEFF G, DE BOCK F, FOELDVARI I *et al.*: Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. *Ann Rheum Dis* 2009; 68: 519-25.
61. LOVELL DJ, RUPERTO N, GOODMAN S *et al.*: Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med* 2008; 359: 810-20.
62. RUPERTO N, LOVELL DJ, QUARTIER P *et al.*: Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet* 2008; 372: 383-91.
63. ILOWITE N, PORRAS O, REIFF A *et al.*: Anakinra in the treatment of polyarticular-course juvenile rheumatoid arthritis: safety and preliminary efficacy results of a randomized multicenter study. *Clin Rheumatol* 2009; 28: 127-37.
64. HENRICKSON M, REIFF A: Prolonged efficacy of etanercept in refractory enthesitis-related arthritis. *J Rheumatol* 2004; 31: 2055-61.
65. TSE SM, BURGOS-VARGAS R, LAXER RM: Anti-tumor necrosis factor alpha blockade in the treatment of juvenile spondylarthropathy. *Arthritis Rheum* 2005; 52: 2103-8.
66. Sulpice M, Deslandre CJ, Quartier P: Efficacy and safety of TNFalpha antagonist therapy in patients with juvenile spondylarthropathies. *Joint Bone Spine* 2009; 76: 24-7.
67. VAN DER LINDEN S, VALKENBURG HA, CATS A: Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York Criteria. *Arthritis Rheum* 1984; 27: 361-8.
68. RACHELEFSKY GS, TERASAKI PI, KATZ R, STIEHM ER: Increased prevalence of W27 in juvenile rheumatoid arthritis. *N Engl J Med* 1974; 290: 892-3.
69. EDMONDS J, MORRIS RI, METZGER AL *et al.*: Follow-up study of juvenile chronic polyarthritis with particular reference to histocompatibility antigen W. 27. *Ann Rheum Dis* 1974; 33: 289-92.
70. SCHALLER JG, OCHS HD, THOMAS ED *et al.*: Histocompatibility antigens in childhood-onset arthritis. *Pediatr* 1976; 88: 926-30.
71. ANSELL BM, BYWATERS EG: Diagnosis of "probable" Still's disease and its outcome. *Ann Rheum Dis* 1962; 21: 253-62.
72. ROSENBERG AM, PETTY RE: A syndrome of seronegative enthesopathy and arthropathy in children. *Arthritis Rheum* 1982; 25: 1041-7.
73. JACOBS JC, JOHNSTON AD, BERDON WE: HLA-B27 associated spondyloarthritis and enthesopathy in childhood: clinical, pathologic and radiographic observations in 58 patients. *J Pediatr* 1982; 100: 521-8.
74. HALL MA, BURGOS-VARGAS R, ANSELL BM: Sacroiliitis in juvenile chronic arthritis: a 10-year follow-up. *Clin Exp Rheumatol* 1987; 5 (Suppl.): S65-7.
75. SHEERIN KA, GIANNINI EH, BREWER EJ *et al.*: HLA-B27-associated arthropathy in childhood: long-term clinical and diagnostic outcome. *Arthritis Rheum* 1988; 31: 1165-70.
76. FLATO B, SMERDEL A, JOHNSTON V *et al.*: The influence of patient characteristics, disease variables, and HLA alleles on the development of radiographically evident sacroiliitis in juvenile idiopathic arthritis. *Arthritis Rheum* 2002; 46: 986-94.
77. CALABRO JJ: Clinical aspects of juvenile and adult ankylosing spondylitis. *Br J Rheumatol* 1983; 22 (Suppl. 2): 104-9.
78. HÄFNER R: [Juvenile spondylarthritis. Retrospective study of 71 patients][Article in German] *Monatsschr Kinderheilkd.* 1987; 135: 41-6, 77.
79. HUSSEIN A, ABDUL-KHALIQ H, VON DER HARDT H: Atypical spondyloarthritis in children: proposed diagnostic criteria. *Eur J Pediatr* 1989; 148: 513-7.