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REVIEW

The clinical presentation in adulthood of juvenile idiopathic arthritis

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ABSTRACT

Juvenile idiopathic arthritis (JIA) is a chronic systemic inflammatory disease, which affects children and adolescents, characterized by significant differences when compared to inflammatory rheumatisms in adulthood. Today, in a panorama enriched in the last decades with great improvements in the diagnostic and therapeutic field, a far from negligible portion and an increasing number of patients with JIA require the continuation of treatments in adulthood. This specific population of patients, given the high incidence of extra-articular manifestations, residual irreversible disabilities, comorbidities related to an inflammatory process and extended immunosuppressive treatments during the age of development, requires precise attentions in the follow-up and a multidisciplinary approach characterized by different clinical, psychological and social aspects.

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The care of adult patients with rheumatic diseases that started and were diagnosed in childhood represents a part of the daily increasing clinical rheumatological practice. In recent years, the international scientific literature has reiterated that the knowledge of clinical presentation, treatment and follow-up in adulthood of the subjects affected by rheumatic diseases with pediatric onset is worthy of more research, better clinical classifications and therefore further long-term studies.[1]

Juvenile idiopathic arthritis (JIA) records an incidence of 2 to 20 cases per 100,000 inhabitants each year. As of today, many authors agree that this is not a single disease as it constitutes a heterogeneous group of conditions, each of them presumably having distinctive genetic and physio-pathological substrates.[2] Although it has not yet been fully understood, it is hypothesized there is a genetic predisposition (as well as in many other conditions) that would play a major role in the development of a proinflammatory response to self-antigens following exposure to a hypothetical environmental trigger

The most common form of JIA is the oligoarticular one (50-60%), strictly followed by polyarticular (30-35%) and systemic forms (10-20%).[3] Regarding the form of arthritis-enthesitis, due to classification difficulties, the estimate of its frequency ranges from 3 to 25%.[3, 4] Psoriatic arthritis in children, unlike their adult-onset counterpart, is much rarer: it constitutes 3-4% of the cases of JIA.[5] The enthesitic form is the one with the most similar clinical approach to the adult-onset spondyloarthritis and for this reason many authors consider it a separate clinical

entity.[6] Systemic arthritis is the form that most distinguishes itself from others for pathogenesis and clinics, as it can have a very unfavourable course, with the chance of onset of the Macrophage Activation Syndrome in 5% of the cases.[7]

All joints can potentially be involved, both in onset and during the course, with the larger ones, such as knees, hips and ankles, showing a higher frequency of involvement than rheumatoid arthritis. It is always necessary to consider that in the paediatric population the inflammation in the large joints stimulates their growth at first but its perpetuation induces an early ossification of the growth cartilage with a consequent premature arrest of bone growth at the joint, thus hesitating in a shortening of the affected limb and residual dysmetria in adulthood.[2]

In the last two decades, the most significant long-term outcome analyses have shown that the very early age of onset of disease (before the age of 5-6) and the positivity of rheumatoid factors and antibodies against citrullinated peptide (ACPA) are two negative prognostic factors which also correlate with a worse radiographic evolution of the pathology.[8-10]

As of today, follow-up studies of patients with JIA that lasted more than 20 years are very rare,[11] and previous studies are difficult to interpret or compare due to the different definitions of remission, disability and diagnostic classifications.[12-14]

Selvaag *et al.* in 2016[12] reported that 41% of patients with JIA preserve a persistent state of illness (intended as an active disease or a remission state during systemic immunomodulatory therapy) 30 years after diagnosis and that in 32% of patients an extra-articular manifestation has an onset regardless of clinical parameters showing low disease activity at joints.[15]

In the study by Oliveira Ramos of 2016[13] the percentage of patients who do not achieve remission in adulthood is even higher (50-67%), proving how JIA is not a self-limiting disease for a substantial portion of patients.

An adult rheumatologist, according to Coulson *et al.*,[15] must always keep in mind that in this population the acute phase reactants can more frequently be negative even in a phase of active disease compared to chronic adult rheumatisms; moreover, an adult rheumatologist needs to consider the macrophage activation syndrome as a rare but possible complication of JIA, especially in systemic forms. It is also essential to ensure that the patient has been adequately vaccinated to prevent an infection in adulthood (chicken pox, measles or rubella) from triggering a worsening of the clinical situation.

When they reach adulthood, patients diagnosed with JIA have comorbid profiles intrinsically correlated to both the chronic inflammatory processes that they have since childhood and to immunomodulatory treatments that lasted during the developmental age.[16-18] In 2013, a study by Raab[18] has documented that 60 to 65% of patients report at least one comorbidity, the most frequent of which is osteoporosis, followed by haematological pathologies and mood disorders which are mainly depressive.

Although the onset of uveitis de novo in adulthood is not frequent, a recurrence of uveitis that occurred in childhood is shown in about half of patients when adult.[19]

Furthermore, there is an increased incidence of irreversible sequelae and disabilities compared to rheumatic patients with an onset of disease in adulthood: more than one third of such patients report at least one of the following JIA-related disabilities:[18, 20]

- somatic dwarfism (Still-like dwarfism);
- dysgnathia (especially micrognathia, due to the involvement of the temporomandibular joint, which gives the typical "bird-like" profile to the affected person);
- ankylosis of the joints;
- pathologic fractures due to osteoporosis;
- iatrogenic ocular complications (subcapsular cataract, glaucoma);
- secondary amyloidosis, with risk of evolution towards renal failure.

For all these reasons, this population of patients inevitably requires specific attention and proper follow-ups.

In the most recent literature, the need for studies and analyses to better understand the pathogenetic basis of these pathologies is emphasized as the necessity for organizational and assistive models dedicated to the Transitional Care, *i.e.* the delicate phase of transition from pediatric care to the one of the adults which can favor

TABLE I.—*Juvenile idiopathic arthritis evolution and course in adulthood.*

Persistent state of illness 30 years after diagnosis (active disease or remission state during systemic immunomodulatory therapy)
• 41% of the patients according to Selvaag *et al.*[12]
• 50-67% of the patients according to Oliveira Ramos[13]
Extra-articular manifestations onset in adulthood:
• About 32% of the patients[12]
Comorbidity profile
• 60 to 65% of patients shows at least one comorbidity[18]
• Metabolic and cardiovascular risk increased when compared to normal population[16]
Irreversible sequelae of disease
• 30-35% of the patients show at least one consequence of disease and/or a disability related to JIA[20]

not only its continuity but also the results of the treatments.[1]

As of today, there are numerous debates concerning the diagnosis, the characterization and the serological-clinical correlations of the disease in adulthood: if the association ANA-uveitis is a long-developed topic, the contemplation of antibodies such as RF and ACPA as predictors is way more recent. A sub-population of patients that may benefit from a more aggressive treatment as soon as the diagnosis is done is therefore coming to be defined. Literature concerning the evolution of serological profiles of these autoantibodies is limited to date; the change of the serological profile of these autoantibodies from diagnosis to adulthood, the chance of seroconversion (in both positivization and negativization) and if they are somehow linked to clinical progress are still incomplete elements (Table I).[12, 13, 16, 18, 20]

Clinimetric evaluation of disease activity

Pediatric rheumatologists, in order to optimize the management of juvenile idiopathic arthritis, have introduced for quite some time the use into clinical practice of disease activity measurement systems which have been developed, validated and approved by the international scientific societies of this clinical area.

In 2009, Consolaro *et al.*[21] developed a score scale to measure disease activity, called the Juvenile Arthritis Disease Activity Score (JADAS). Validated in different countries all over the world, this score is the most reliable tool to date in order to follow the course of the disease over time and its response to treatments.

The JADAS Score consists of four areas of evaluation that concern: an overall opinion of the doctor on the activity of the disease (Global Health doctor), a global assessment of the patient or parent about the wellbeing of the child (Global Health patient), the value of the normalized ESR and the number of joints in which the disease is active (where "active disease" means the presence of swelling or, if absent, a functional limitation together with pain in movement).

Several versions of the JADAS score have been developed (JADAS10, JADAS27 and JADAS71) that differ in the number of joints considered.[22] The measurement system most commonly used both in clinical practice in specialized pediatric centers and in scientific work is currently the JADAS27. Its main limitations are the absence of evaluation, in this count, of possible extra-articular manifestations, the absence of a radiological evaluation of joint damage and the absence of validation in adulthood.[23] In fact, JADAS is an index mostly unknown to adult rheumatologists since it is not part of the clinimetric apparatus commonly used in clinical practice. Adult patients with JIA are therefore usually evaluated with the clinimetric scores developed for chronic adult rheumatic diseases and currently there is no consensus on which of these scores should be favored in this patient population, so that the choice is destined to autonomous preference from center to center (Figure 1).

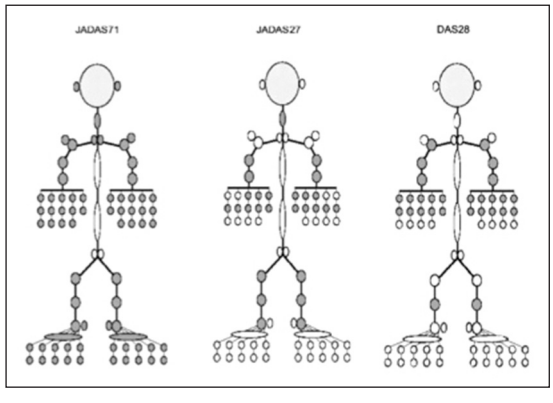

Figure 1.—Articulations considered by different score: JADAS71, JADAS27 and DAS28.
JADAS: Juvenile Arthritis Disease Activity Score; DAS: Disease Activity Score.

Conclusions

The care of adult patients with rheumatic diseases that started and were diagnosed in childhood represents a part of the daily increasing clinical rheumatological practice. More and more evidence is acquiring the notion that it is wrong to reclassify the diagnoses of these patients in adulthood with the adult counterpart of chronic inflammatory rheumatisms[24] and it is actually adequate to continue with the categories typical of the childhood.

In the most recent literature, the need for long-term studies and analysis of JIA in adulthood is emphasized in order to better understand the pathogenetic basis of these pathologies as it is reiterated the need for proper organizational and welfare models dedicated to the delicate phase of transition from pediatric care to adult care, which may favor the continuity and the results of the treatment itself.[1]

The importance of understanding the progression of this disease in adulthood lies in the possibility of adding useful knowledge to continue the study of etiopathogenesis; this element may favor a better classification and consequently improve the therapeutic choices in this pathology as it could favor a more active communication between pediatric and adult care specialists.[13]

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