Long-term outcomes in a cohort of patients with juvenile idiopathic arthritis: serological phenotypes and disease activity in adulthood

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Abstract

In a scenario characterised by diagnostic and therapeutic improvements, an increasing number of juvenile idiopathic arthritis (JIA) patients require ongoing care into adulthood. Deepening the long-term study on JIA is fundamental in order to expand pathogenic knowledge, optimize treatment options and favour an active communication between paediatric and adult care-specialists. This study dealt with adult patients affected by JIA. The main objectives were: i) to analyse the serological profile to examine possible seroconversions in adults; ii) to evaluate the association between antibodies and disease activity; iii) to investigate the correlation between antibodies, diagnostic subgroups and disease activity. Sixty-eight patients were selected. A positive rheumatoid-factor and anti-citrullinated-peptides-antibodies tests were found both at diagnosis and in adulthood (P<0.05). Their association with the polyarticular subgroup persisted in the long term (P<0.05) and they associated with a higher disease activity in adulthood assessed with both JADAS27 and SDAI. At diagnosis, 45.6% of patients were ANA positive, while only 13.2% stayed positive in adulthood (P<0.05). These results may highlight the need to verify in

adulthood the presence of ANA in those patients with JIA with ANA positivity at diagnosis.

Introduction

The treatment of adult patients with rheumatic diseases with onset and diagnosis during childhood represents an increasingly important part of daily rheumatological clinical practice. In recent years, the international scientific literature has reiterated that knowledge of clinical presentations, as well as treatments and long-term follow-ups on patients with rheumatic diseases with paediatric onsets is worth both further long-term investigations and better clinical classifications.[1,2] Long-term studies of juvenile idiopathic arthritis (JIA) in adult patients are essential to acquire a better insight into the pathogenesis of the disease, to improve treatment options and to favour a more active communication between paediatric and adult care specialists.[3,4]

JIA is a chronic inflammatory disease with unknown aetiology whose clinical onset is set before the age of sixteen. It includes a heterogeneous group of conditions, for which many authors agree on the existence of a distinctive genetic and physiopathological substrate.[5-7]

These conditions are summarized in the 2001 ILAR classification, which is currently used in both clinical practice and scientific studies as it recognizes seven diagnostic subtypes based on the clinical characteristics developed in the first six months after the disease onset: systemic JIA, oligoarticular JIA (persistent-extended), polyarticular RF-positive JIA, polyarticular RF-negative JIA , psoriatic JIA, enthesitis-related JIA, undifferentiated JIA.[8]

The most common yet feared extra-articular manifestation of JIA is ocular involvement: uveitis is present in 13-34% of patients with the disease, despite their diagnostic subtype. Uveitis particularly affects oligoarticular JIA patients;[9,10] nevertheless, it may still appear during adulthood even with immunosuppressive treatments[11] and it can result in different degrees of irreversible visual impairments. Moreover, the onset and the severity of such uveitis proved to be unrelated with a more intense concomitant inflammatory articular involvement.[12,13]

Long-term follow-up studies are still not numerous and previous studies are often difficult to interpret or compare because of different definitions of remission and disability as well as the different diagnostic classifications they use.

Current literature reports up to 67% of patients with active disease 30 years after diagnosis (active disease or in remission during systemic immunosuppressive therapy),[3] 32% of patients with a new extra-articular manifestation with adult onset[4] and a

high comorbidity rate correlated with a chronic inflammatory process with childhood onset and ongoing immunosuppressive treatments during the age of development.[14,15] It also shows half of the patients with uveitis in paediatric age that relapses during adulthood[16] and an increased incidence of sequelae and irreversible disabilities compared to rheumatic patients with adult-only disease onset.[17,18] In recent years, however, thanks above all to diagnostic and therapeutic advances, disabilities registered in adulthood are considerably decreasing.

In 2009 paediatric rheumatologists validated a rating scale called Juvenile Arthritis Disease Activity Score (JADAS), intended to assess the trend of the disease and the responses to treatments over time.[19] One of the limits of this score is the lack of validation in adult patients. As of today, there is no consensus on which score is to be preferred on this population and each centre is thus entitled to an independent choice.

No antibody is known to have a pathogenic role. Clinical records show that 30 to 50% of children with JIA have a positive test for antinuclear antibodies (ANA).[20,21] Even though the clear majority of patients (70-90%) who develop uveitis show antibody positivity,[22] in the literature such correlation is still debated.[10,21,23] Consequently, there is no subcategory of the population with a higher risk of developing extra-articular manifestations requiring different follow-ups.

Rheumatoid factor (RF) is present in 5 to 10% of children with JIA, and almost all the positive patients belong to the polyarticular subtype. As a result, a specific RF-positive polyarticular subgroup has been distinguished.[7,24] The presence of RF is correlated with a more severe long-term disability, a higher disease progression rate and worse temporomandibular and coxofemoral joint involvement. Moreover, these joints are usually not involved in rheumatoid arthritis, which is a further reason not to mistake RF-positive JIA for a form of early-onset rheumatoid arthritis.[25]

Anti-citrullinated peptide antibodies (ACPA) are still widely studied in this population. They are found in 14-24% of patients at diagnosis[26] and their presence is correlated with concomitant RF positivity, with polyarticular JIA and with worse outcomes.[27-29] As of today, the seroconversion of such antibodies in adults is not clear, as it is assessed only by a few studies.[30]

In the last few years, knowledge of this disease has considerably increased, with a positive effect on both therapy and prognosis. This element has contributed to making the transition from paediatric to adult health care facilities more relevant. This process is now referred to as *transition of care* and in 2016 EULAR (European League Against Rheumatism) published its recommendations for transitional care in young patients with rheumatic diseases in collaboration with PRES (Paediatric Rheumatology European Society);[1] these recommendations are based on experts' consensus whose main goal is to simplify the clinical management and administration of the transition. The end of this process is to guarantee both maintenance and reinforcement of the clinical results obtained during the treatment in childhood and to create a consistent framework of long-term clinical information in order to promote scientific knowledge of the disease as well as an evidence-based clinical practice.[31-33]

The present study was carried out on adult patients with juvenile idiopathic arthritis. Its main goals were: i) to analyse the serological profile (RF IgM, ACPA IgG, ANA) of the patients in order to investigate any seroconversion in adult age versus childhood; ii) to investigate the presence and the conservation of the correlation between antibodies and diagnostic subgroups in adult age; iii) to assess the correlation between antibodies and disease activity; iv) to analyse the correlation between antibodies, diagnostic subgroups and disease activity.

Materials and Methods

Sixty-eight patients were consecutively selected at the Rheumatology Clinic of the Città della Salute e della Scienza University Hospital of Turin from January 1st, 2017 to March 1st, 2018.

All the patients had a diagnosis of JIA, made within the previous 20 years, complying with the 2001 ILAR criteria. The main source of data on medical, clinical and laboratory history was represented by clinical records and by reports of outpatient visits.

A blood sampling was performed to search for ANA, RF and ACPA; clinical data on disease activity were collected, using clinimetric scores JADAS27 and SDAI.

The ANA assay was performed by analysing the samples obtained through indirect immunofluorescence tests on a Hep2 cells substrate (Hep2010, Euroimmun, Lübeck, Germany). The samples with a titre equal to or greater than 1/160 were considered positive.

The serum concentration of RF and ACPAs were measured using EliA solid-phase fluoroenzyme immunoassay (Thermofisher Phadia AB, Uppsala, Sweden) on the Phadia 2500 automated platform and the results were considered positive if over a cut-off of 5 U/mL for RF and 10 U/mL for ACPA, respectively.

All patients included in this study gave their informed consent prior to their inclusion.

Statistical analysis

The analysis was performed with MedCalc (version 17.2) and SPSS (SPSS Inc. Chicago IL, version 18.00). Continuous variables were shown as medians with their range every time they did not belong to a normal distribution as they were plotted with their mean and their standard deviation when normally distributed. The difference among the groups was assessed through nonparametric statistics (Mann-Withney). The categorical variables were described as fractions and percentages, and the prevalence difference was assessed using a χ^2 test (Pearson) or, when appropriate (such as in analysis of clinometric indexes), using McNemar's test and concordance analysis (Cohen's kappa coefficient).

A P value <0.05 was considered significant.

Results

Demographic, clinical and serological characteristics are reported in Tables 1 and 2.

In our cohort, patients were mainly women (54/68, 79.4%).

Mean age was 28 years (19-51) and mean disease duration was 17 years (2-40).

Positivity for ANA was found in 45.6% of the paediatric population, but only in 13.2% of the same adult cohort (P<0.05). RF positivity was present in 14.7% of patients at diagnosis and in 20.6% of patients in adulthood whilst ACPA positivity was found in 14.7% of cases during childhood and in 17.6% of cases in adult age. RF and ACPA values were unaltered in the adult age without any meaningful seroconversion when compared to childhood. The concurrent positivity for RF and ACPA was observed both at

diagnosis and in adult age (P<0.05), proving to be statistically significant. Further evidence showing how important these two factors are for disease classifications comes from the observation that both RF and ACPA were associated with the polyarticular subgroup in childhood as well as in adulthood (P<0.05), while ANA did not correlate with any diagnostic subgroup either at diagnosis or in adult age (P>0.05).

In this study, data showed a significant negativization of ANA in adulthood: at diagnosis, 45.6% of patients were ANA positive, while in adulthood the ratio of patients positive for ANA decreased to 13.2%. This difference was statistically significant, although worthy of further evaluation and confirmation in larger populations.

The correlation between positivity for RF-ACPA and disease activity, evaluated with JADAS27 and SDAI clinimetric indexes, proved the negative prognostic role of the two antibodies (Figure 1), since they are associated with a higher disease activity in childhood as well as in adulthood.

Discussion and Conclusions

By analysing the results of this study, it was possible to note that the serologic profile of RF and ACPA remained unchanged over time. The presence of the two antibodies correlated with the polyarticular subgroup even in the long term and it was associated with a worse disease outcome.

A substantial number of patients who had positivity for ANA at diagnosis in paediatric age was no longer positive for ANA once adult. This population seems to have undergone a significant seroconversion of ANA in adult age. This data needs further verification in a wider population but may suggest the need for a new assessment of these antibodies in adult age.

In conclusion, we believe it is interesting to report the observation of low RF and ACPA antibody titers observed in adult age (up to 45 U/mL for RF and 400 U/mL for ACPA, respectively). The reference in literature of low ACPA titers at diagnosis of JIA in paediatric age[28] may suggest an increase of antibody titers over time that may be irrelevant. It would be important to complete further studies on this topic and perform a quantitative analysis of the possible trends of RF and ACPA in order to increase knowledge of the pathogenesis of the disease.

As the study got started, the disease activity calculated with both JADAS27 and SDAI reported a scenario in which most patients were in remission or low disease activity (Table 3).

As for the correlations between positivity for RF-ACPA and disease activity, quantified with clinimetric indexes JADAS27 and SDAI: the association between RF and ACPA was always statistically related to a higher disease activity, which implied a higher mean of their respective clinimetric scales (P<0.05) (Figure 1). These data, in

Table 1. Demographic and clinical characteristics of patients (n=68).

Female n (%)	Age of assessment (range)	Age at diagnosis (range)	Disease duration (range)
54 (79.4%)	28 years (19-51)	11 years (1-16)	17 years (2-40)

Diagnostic subgroups	Systemic JIA n=10 (14.7%)	Oligoarticular JIA n=28 (41.2%)	Polyarticular JIA n=20 (29.4%)		Psoriatic JIA n=3 (4.4%)	Enthesitis-related JIA n=7 (10.3%)
			RF positive n=9	RF negative n=11		
Female n (%)	6 (60%)	13 (46.4%)	9 (100%)	9 (81%)	2 (67%)	2 (28.5%)
Uveitis	0	8 (28.6%)	0	2 (18%)	0	2 (28.5%)

sd, standard deviation; JIA, juvenile idiopathic arthritis; RF, rheumatoid factor.

Table 2. Serological characteristics of patients (n=68).

	At diagnosis	At assessment
Anti-nuclear antibodies (ANA)	31 (45.6%)	9 (13.2%)
Rheumatoid factor (RF)	10 (14.7%)	14 (20.6%)
Anti-citrullinated-peptides-antibodies (ACPA)	10 (14.7%)	12 (17.6%)

Diagnostic subgroups	Systemic JIA n=10 (14.7%)	Oligoarticular JIA n=28 (41.2%)		Polyarticular JIA n=20 (29.4%)		Psoriatic JIA n=3 (4.4%)	Enthesitis-related JIA n=7 (10.3%)
		Persistent n=14	Extended n=14	RF + n=9	RF – n=11		
ANA pos. at diagnosis in adulthood	3	10	7	4	4	1	2
	1	3	1	2	1	0	1
RF pos. at diagnosis in adulthood	0	0	1	9	0	0	0
	0	1	1	9	1	1	1
ACPA pos. at diagnosis in adulthood	0	1	1	8	0	0	0
	0	1	2	9	0	0	0

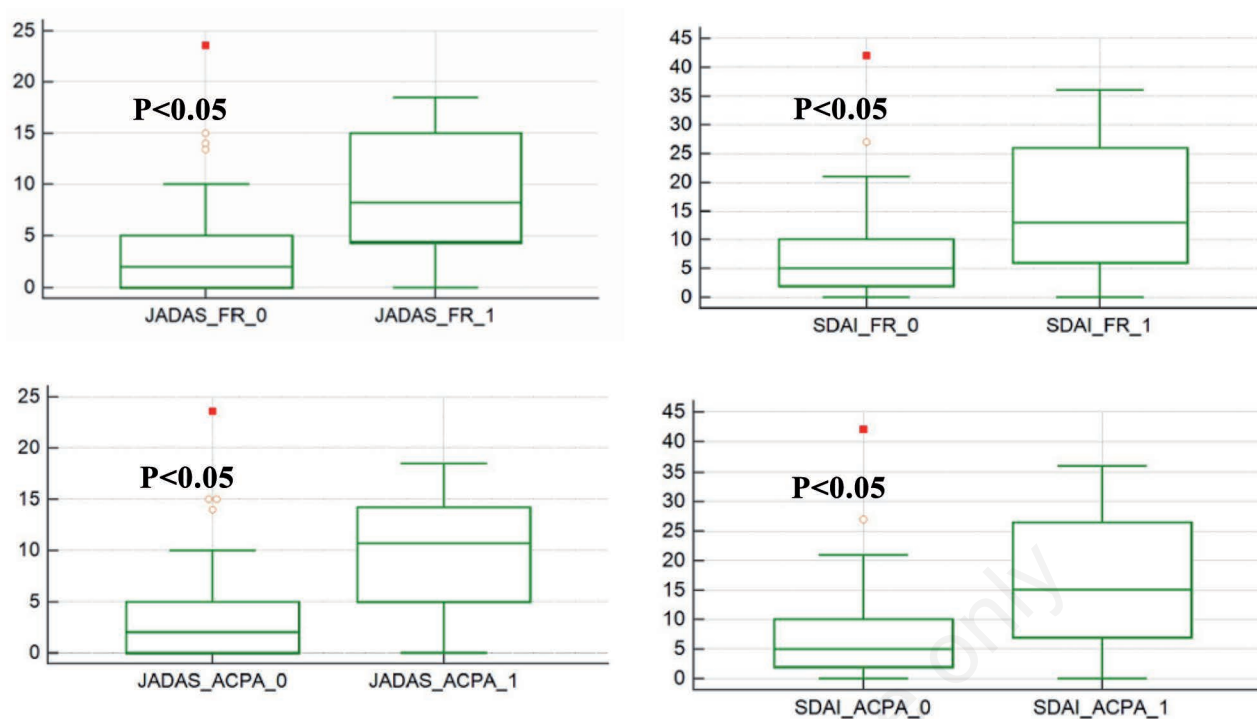JIA, juvenile idiopathic arthritis; pos., positivity.

Figure 1. Disease activity correlated with the presence ("1")/absence ("0") of rheumatoid factor (FR) and anti-citrullinated peptides antibodies (ACPA). Considered cut-off of 5 U/mL for RF and 10 U/mL for ACPA, respectively.

Table 3. Distribution of the patients (n=68) according to their disease activity calculated with different clinimetric indexes (JADAS27, DAS28, CDAI, SDAI).

Disease activity	JADAS27		DAS28		CDAI		SDAI	
Remission	<1	22	<2.6	44	<2.8	34	≤3.3	26
Low	≤2.7	10	≤3.2	13	≤10	26	≤11	26
Moderate	<6	19	≤5.1	10	≤22	7	≤26	11
High	≥6	17	>5.1	1	>22	1	>26	5

line with the literature, confirm the negative prognostic role of the RF which is now widely proven and recognized, and it supports the role of ACPA in identifying a more aggressive pathology; on such elements there are currently fewer studies, especially those concerning JIA population in adulthood.

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