Detection of synovitis by ultrasonography in clinically inactive juvenile idiopathic arthritis on and off medication

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Abstract

Objective

To determine the prevalence of abnormalities detected by ultrasonography (US) in children with juvenile idiopathic arthritis (JIA) showing clinically inactive disease (ID) on medication and off medication.

Methods

Inclusion criteria: 1) JIA patients, 2) clinician-determined ID, 3) JIA drugs withdrawal or stably dosed modified anti-rheumatic drugs (DMARDs) therapy for at least 6 months prior to inclusion, 4) biologics naïve patients.
Clinical and US assessments were performed on 44 joints, which were scored for grey-scale (GS) synovitis and Power Doppler (PD) signal. PD signal inside intra-articular synovium or tendon sheath was considered as inflammatory activity.

Results

Thirty-four patients were included, of whom 23 patients were labelled as ID on medication and 11 patients without medication. The duration of the current episode of ID at the inclusion time was 9.5 months. Although it was longer for the group off medication there was no significant difference between the two groups (p=0.06). Thirteen patients presented US findings. Number of US-detected synovial abnormalities was higher in patients on medication, but there were no significant differences between both groups in the detection of GS synovitis (p=0.86), GS tenosynovitis (p=0.78) and PD signal (p=0.38). Out of 37 joints presenting US-determined GS-synovitis, 18 joints showed PD signal.

Conclusion

Our study provides evidence of synovitis and tenosynovitis on B-mode US in JIA patients with clinical inactivity. In addition, inflammatory activity upheld by power-Doppler has been shown in a few joints from patients on medication.

Key words
juvenile idiopathic arthritis, ultrasonography, synovitis, inactive disease

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Introduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of arthritides with chronic synovial inflammation that can lead to structural damage. The main objective of JIA therapies is to induce completed disease control in order to avoid disability into adulthood. Nevertheless, until recently, it has been difficult to achieve it in most forms of JIA. Children with arthritis can experience extended periods of low level activity and inactive disease (ID). In the last years, a set of preliminary clinical criteria for JIA patients was developed, in order to enable the classification of patients in the different states of disease control (*i.e.* ID, clinical remission with medication, and clinical remission without medication) (1).

The advances in therapeutic effectiveness have created a need for looking for imaging tools that describe more precisely the clinical state of ID and clinical remission in children with JIA. Over the past decade, a growing number of studies have proven the usefulness of ultrasonography (US) for detecting synovitis in JIA (2, 3). Therefore, the well-known advantages of US in the paediatric population, make it an ideal tool not only for diagnosis, but also for therapy monitoring (4, 5). Studies on JIA disease remission have rarely included imaging assessment (6, 7). This bedside imaging technique might cover the gap between the clinical assessment and the real state of the disease. Achievement of sustained disease control is not usual in the short time frame and relapses after therapy discontinuation have been reported (8). Since relapses may be influenced by residual synovial inflammation at the time of therapy withdrawal, the objective of this study was to determine the prevalence of abnormalities detected by US in children with clinically inactive JIA on medication and off medication.

Patients and methods

Patients

This is a cross-sectional multicentre study including children with JIA who were recruited from six Spanish rheumatology centres between June 2010 and December 2011. All participants were referred from paediatric rheumatologist outpatient clinics by their usual clinicians. Inclusion criteria were the fulfilment of the International League of Associations for Rheumatology (ILAR) revised criteria for JIA (9), age from 4 to 16 years, clinically ID determined by clinician basing on Wallace criteria of ID (1), JIA drug withdrawal or stably-dosed modified anti-rheumatic drugs (DMARDs) therapy for at least 6 months before enrolment, no previous biologic therapy experience and no intra-articular steroid injections in the last 6 months.

The study was approved by the local ethics committees of all participating centres and conducted in accordance with the Declaration of Helsinki and the International Guidelines for Ethical Review of Epidemiological Studies. Parents gave informed consent for their children to participate. Signed assent forms according to their age and knowledge was obtained from the children themselves.

Clinical assessment of disease

First, the clinical ID was determined by their usual clinicians based on the Wallace criteria of ID – no joints with active arthritis (1), no fever, rash, serositis, splenomegaly, generalised lymphadenopathy attributable to JIA, no active uveitis, normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and the physician's global assessment of disease activity indicating no disease activity. Later, the clinical investigator at each centre confirmed the fulfilment of the inclusion criteria.

The clinical visit was performed by the same clinical investigator (paediatric rheumatologist) from each centre, each having at least six years of clinical rheumatology practice. Disease-related information included: age, sex, ILAR category, disease duration, number of ID states and their duration, and treatment (*i.e.* non-steroidal anti-inflammatory drugs (NSAIDs) oral steroids, DMARDs) for JIA, and 10 cm visual analogue scale (VAS) for the physician's assessment of global disease activity (PhGA VAS), for the patient's or the parent's assessment of joint pain

(Pain VAS) and for patient's or parent's global assessment of disease activity (PGA VAS). The Childhood Health Assessment Questionnaire (CHAQ) was used to assess functional status (10).
Swollen, tender and restricted painful motion joint counts were assessed on physical examination. Twenty-two joints were bilaterally examined (*i.e.* shoulder, elbow, wrist, metacarpophalangeal (MCP), proximal interphalangeal (PIP) of the hands, hip, knee, ankle, tarsal and metatarsophalangeal (MTP) joints). The normality of the laboratory parameters (*i.e.* ESR and CRP) was determined at time of study inclusion at each centre's laboratory. The presence of rheumatoid factor (RF) and antinuclear antibodies (ANAs) were also included.

Radiographic assessment of disease
Conventional radiography was used for looking for joint damage. An experienced musculoskeletal radiologist paying attention to joint space narrowing and erosions reviewed radiographic studies at each centre. The radiologist was aware of the JIA diagnosis, but not the clinical and US findings.
In addition to plain radiographs of the clinically involved joints, the anteroposterior radiographs of both knees, and the posteroanterior radiographs of the hands and feet were obtained in those participants with a disease duration longer than 1 year according to literature recommendations (11, 12).

Ultrasonographic examination
The US examination was performed on the same day of clinical visit by an experienced ultrasonographer at each centre, each having more than five years of experience, who was blinded to clinical findings. All children were first investigated on B-mode US and afterwards on Power Doppler US -just in case of abnormal findings on B-mode. B-mode US was performed to detect structural abnormalities (*i.e.* effusion and synovial hypertrophy in the joint recess and tendon sheath, and bone erosion) and PD was used for identifying synovial hyperaemia. All centres used Logiq e-US scanner (General Electric Medical Systems, GE, Kyunngi, Korea) with a 12L MHz multifrequency linear transducer for US assessments. Prior to the study, *GE personnel* standardised the technical parameters for US assessment in all the machines. The PD settings were the following: the pulse repetition frequency (PRF) range was from 600 to 800 Hz depending on the joint examined, the PD gain was set at the highest level at which PD signal did not appear under the bony cortex, and low wall filter.

Evaluation of US images
US images were evaluated in real time and the data were registered in a specific form developed for this study. The Outcome Measures in Rheumatology Clinical Trials (OMERACT) definitions of pathology in rheumatoid arthritis (RA) were used to assess joint effusion (Eff), synovial hypertrophy (SH) and tenosynovitis (13). Joint synovitis was considered according to the presence of both or either of the two components (SH or Eff) of synovitis. The US evaluation included bilateral scanning of the same 22 joints clinically evaluated in each patient (Table I).
Firstly, each joint was scored for grey-scale (GS) synovitis in B mode US. Because of the variable age-related US imaging of the epiphyseal cartilage, we used a consensual scoring system of paediatric synovitis for the elbow, radiocarpal, tibiotalar, mid-foot and the finger joints previously reported in the literature (14). It consisted of a 4-point semi-quantitative scale of GS synovitis: 0, absence, normal joint recess; 1, mild, synovitis filling the joint recess between periarticular epiphyses that leads to change from the angle-shaped recess to a plateau-shaped recess; 2, moderate, convex shape of the joint recess without extension over the bone diaphysis; and 3, marked, convex shape of the joint recess with extension to at least one of the bone diaphyses (Fig. 1). The knee joint was scored according to the RA scoring system (14, 15). Depending on the capsular distension of the hip, it was subjectively scored into 4 grades: normal, mild synovitis, moderate synovitis and severe synovitis (16). The shoulder was scored in a dichotomous assessment (presence or absence of synovitis). Similarly, tenosynovitis was scored in a dichotomous assessment.
Positive PD signal was defined as the presence of synovial vascularisation inside synovial hypertrophy in the joint or tendon sheath. It was scored in a dichotomous assessment (Fig. 2). As tiny Doppler signals may be occasionally detected at the epiphyseal cartilage due to the growing skeleton's feeding vessels, for the purpose of the current study only synovial hyperaemia was considered as a pathological finding.
Because there are no published US scanning protocol specifically designed for children, US examinations were performed according to an approach used previously for children (17). US abnormalities must be documented on two perpendicular (longitudinal and transverse) planes. The US image acquisition time was approximately 35-40 minutes per patient. Information regarding assessment of intraobserver reliability of ultrasound evaluation has been reported previously (14). As

Table I. Synovial areas evaluated on power Doppler ultrasound at each joint.

Shoulder	Posterior recess
Elbow	Anterior and posterior recesses
Wrist (radiocarpal joint)	Dorsal carpal recesses
	Extensor digitorum tendon sheath
Hip	Anterior recess
Knee	Suprapatellar recess
	Medial and lateral recesses
Ankle	Dorsal tibiotalar recess
Talonavicular	Dorsal recess
MCP, PIP of hands and MTP	Dorsal recess
	Palmar/plantar recess
	Flexor fingers tendon sheath

MCP: metacarpophalangeal; PIP: proximal interphalangeal; MTP: metatarsophalangeal.

US examination of a child by all ultrasonographers of study was not feasible, interobserver variability on US findings was determined scoring static images; For the purpose of determining it, the reading of at least 27 images by the six ultrasonographers was planned. This sample size would allow estimating a Kappa reliability coefficient greater than or equal to 0.85, with a significance level of 95% and a power of test of 20%. The proportion of positive classifications between observers would be assumed to be 5%. A replacement rate has not been estimated. The observers scored 30 static images with different degrees of disease activity from JIA patients attended in the coordinating investigator hospital, randomly chosen by the coordinating investigator of the study (PC).

Statistical analysis

Statistical analysis was performed using SPSS statistical software, version 17.0 (SPSS, Chicago, IL, USA). The results were expressed as mean (standard deviation, SD) and median (interquartile range, IQR) for normally and non- normally distributed variables, respectively. Comparison of demographic, clinical and US findings between the groups of patients – on medication and off medication – was analysed by Chi-square test or Fisher's exact test in case of qualitative variables. In case of quantitative variables comparison was made by the *t*-test or the non-parametric Mann-Whitney U-test. The statistical package Epidat 3.1 was used for interobserver agreement analysis. Interobserver agreement was evaluated using the Cohen's kappa agreement index (unweighted for dichotomous scoring, presence/absence), the Cicchetti-weighted kappa for semi-quantitative scoring of GS images (score: 0, 1, 2 or 3), while the Jackknife technique was used in order to calculate the confidence interval. The level of Kappa agreement was defined as follows: ≤0.20 = poor, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = good, and 0.81–1 = almost perfect (18, 19). All tests were 2-sided and a *p*-value less than 0.05 was considered statistically significant.

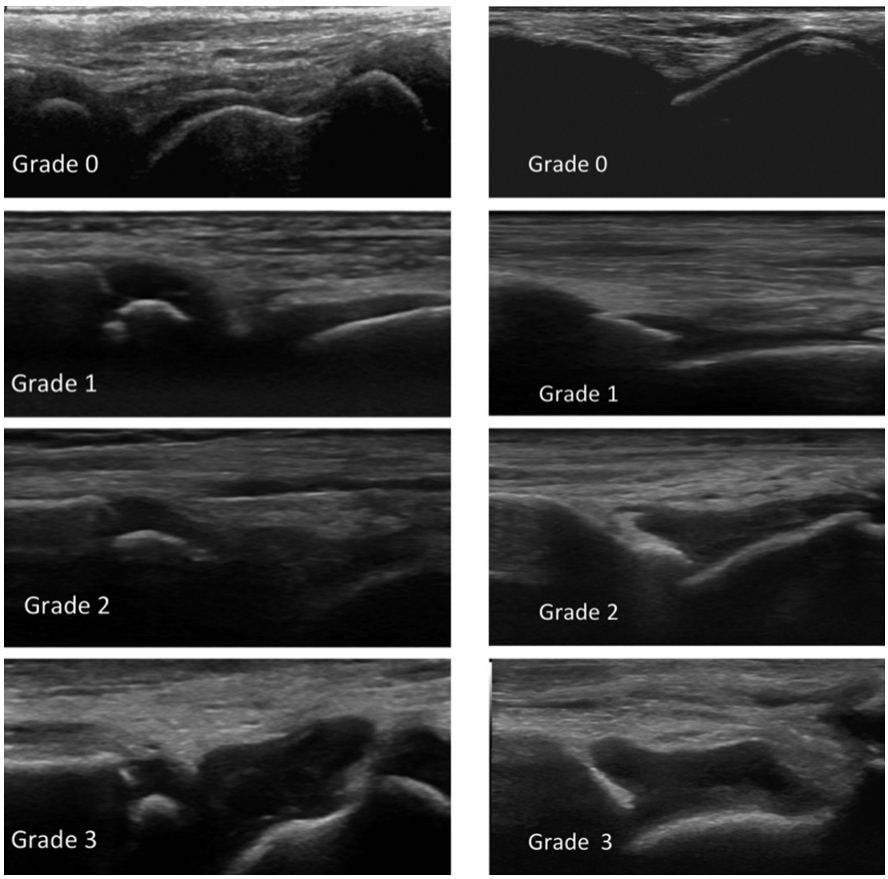

Fig. 1. Scoring systems used for assessment of grey-scale synovitis.
Longitudinal sonogram of the dorsal tibio-talar joint. Semi-quantitative scoring system for grey-scale synovitis in JIA (in the left side) compared with semi-quantitative scoring system for grey-scale synovitis in adult rheumatoid arthritis (in the right side).

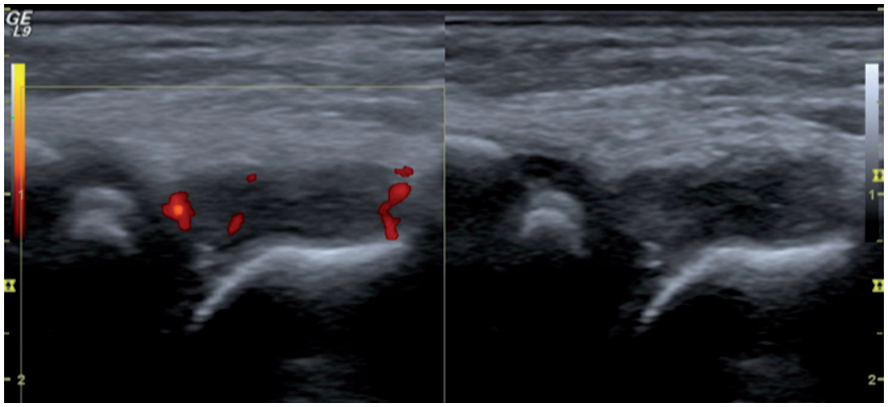

Fig. 2. Scoring system used for assessment of power Doppler (PD) synovitis.
Binary scoring system for PD-synovitis in JIA showed in a longitudinal sonogram of the tibio-talar joint.

Results

Demographic and clinical characteristics of the study population.

A total of 34 patients fulfilling the inclusion criteria were studied. Twenty-three patients with JIA presented ID on medication (IDon) and 11 (32.4%) patients presented ID off medication (IDoff) at the inclusion time (Table II). Table II shows demographic and clinical characteristics of the study patients. Twenty eight (82.4%) patients had oligoarthritis (n=15, persistent and 13, extended) and 6 patients had polyarthritis (2, RF positive and 4, RF negative). All patients had received DMARDs and NSAIDs at some point in their disease. At inclu-

Table II. Demographic and clinical characteristics of the study population.

Variable	Study Cohort (34 patients)	*ID off medication	‡ID on medication	*p*-value
Age, mean (SD) years	9.3 (4)	10 (3.5)	9.3 (4.5)	–
Female / male (%)	28/6 (82/18)	10/1	18/5	–
Disease duration, mean (SD) months	49 (35)	54 (36)	46 (36)	0.068
ID duration of the current ID [(1)], median (IQR) months	9.5 (6–15)	12 (12–24)	8 (6–11)	0.060
ID duration of the last episode of ID [(2)], Md (IQR) months	9 (3–19)	19 (14–30)	4.5 (2.5–12)	0.065
PhGA VAS Md (IQR) months	0 (0–0.1)	0 (0–0)	0 (0–0)	0.063
PGA VAS Md (IQR) months	0 (0–0)	0 (0–0.1)	0 (0–0)	0.74
Pain VAS Md (IQR) months	0 (0–0.1)	0 (0–0.8)	0 (0-0)	0.14
CHAQ median (range)	0 (0–0.63)	0 (0–0.63)	0 (0–0.05)	0.53
ESR (mm/1st h) mean (SD)	9 (6.3)	10.3 (6)	9.3 (8)	0.31
CRP (mg/L) mean (SD)	1 (1.5)	1.2 (1)	1 (0.9)	0.97
Platelets mean (SD)	273.10^3 (66)	283 (64)	259 (69)	0.71
RF positive, n. patients (%)	2 (5.4)			
ANA positive, n. patients (%)	22 (64.6)			

[(1)] Duration of the current episode of ID at the time of study inclusion
[(2)] Duration of the last episode of ID prior to the current episode of ID.
ID: Inactive Disease; *ID on: group of patients having ID on medication; ‡ID off: group of patients having ID off medication; SD: standard deviation; Md: median, IQR: interquartile range; PhGA VAS: visual analogue scale for physician's global assessment of disease activity; PGA VAS: visual analogue scale for patient's or parent's global assessment of disease activity; Pain VAS: visual analogue scale for patient's or parent's assessment of joint pain; CHAQ: Childhood Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; CRP: C reactive protein; RF: Reumatoid Factor; ANA: antinuclear antibodies.

sion time, 17 (74%) patients of the IDon group were receiving oral methotrexate, the remainder were receiving other DMARDs (sulfasalazine, hydroxychloroquine) and none of them were receiving NSAIDs.

Clinical and laboratory findings

Overall, the results of measures of disease activity were all low, with no evidence of significant differences between the two groups (Table II). In addition, 82.4% (n=28) patients showed no functional disability assessed by the CHAQ, but it was mild in the 2.9% (n=1) and varied from mild to moderate in the 14.7% (n=5) of patients. Although duration of the current episode of ID in IDoff group was longer than the IDon group, there was no significant difference between the two groups (p=0.06). About 50% of the participants achieved previously at least one ID episode before the ongoing ID state for enrollment. Overall, four (11.8%) patients attained two previous ID states, five (14.7%) patients attained three, whereas five (14.7%) patients attained more than three ID states. Regarding the number of attained ID states prior to the current episode, there were no significant differences between the two groups (p=0.38).

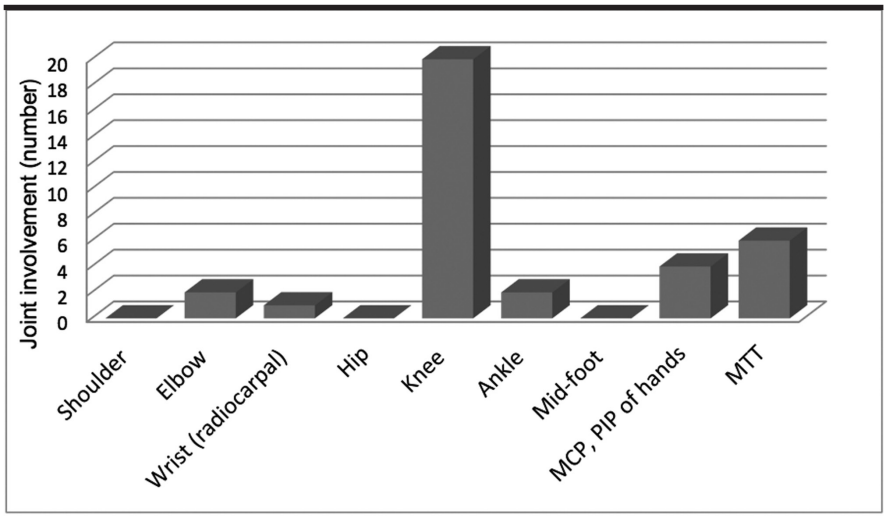

Fig. 3. Distribution of ultrasonographic joint involvement in the cohort of study.
Distribution of grey-scale synovitis revealed by ultrasonographic examination in 37 joints of juvenile idiopathic arthritis patients presenting clinically inactive disease. MCP: metacarpophalangeal; PIP: proximal interphalangeal; MTT: metatarsophalangeal

Radiographic findings

Radiographic studies were performed in 21 (61.8%) patients. Only one patient of the IDon group showed unilateral bone overgrowth in the wrist joint. No erosions were detected in reviewed radiographic studies.

Findings in US examination

In the entire cohort of JIA patients, 38.2% (13/34 patients) had evidence of some synovial abnormalities in US examination. To determine whether medication modified the detection of synovitis, patients were stratified according to JIA treatment withdrawal in 2 groups. Of the 13 patients with US findings, up to 8 patients were into the IDon group, and 5 patients in the IDoff group. Stratifying for ID off medication showed that the number of US abnormalities per patient detected was slightly lower than the IDon group (p=0.36). There were no significant differences between the two groups in the detection GS joint synovitis (p=0.86), GS tenosynovitis (p=0.78) and PD signal (p=0.38).

Up to 1496 joints were examined in the present study. US examination detected 37 (2.5%) joints presenting GS synovitis (Fig. 3). Stratifying for ID off medication showed the joint involvement was lower than the IDon group (IDoff group, 12 joints and IDon group, 25 joints). Out of 37 joints with GS synovitis, 18 (48 %) had PD activity (1.2% of total joints). Nearly all joints with GS synovitis were scored as grade 1, and three joints were scored as grade 2 on B-mode US (the suprapatellar recess in two knees and one thumb metacarpophalangeal joint). Tenosynovitis was detected involving the extensor digitorum tendon at the wrist level and the 2nd-4th finger flexor tendons. PD activity was detected at different anatomical areas of the following joints, the knee (n=10 GS synovitis), elbow (n=2 GS synovitis), ankle (n=2 GS synovitis), wrist (n=2; 1 GS synovitis and 1 tenosynovitis of the extensor digitorum tendon), MCP (n=3; 1 GS synovitis of 1st MCP and the 2nd-4th flexor tenosynovitis), the 3rd PIP and 1st MTP joints. Nearly all patients with PD active synovitis and tenosynovitis were IDon group patients. Structural damage detected as blurring of cartilage without cortical bone irregularities was detected in two patients of IDon group (one knee joint and one ankle joint).

Comparison of ID states and clinical features between patients with US findings and patients without US findings

Overall, patients without US findings (21 patients) achieved longer ID states than did patients with findings (13 patients); median [IQR] months was 10 [3-30] and 8 [6-15], respectively. Nevertheless, there were no significance differences regarding the number and duration of ID states. The two groups were comparable for the remainder clinical features at study entry (data not shown).

Interobserver agreement on US images

The corresponding Kappa values and 95% confidence interval (CI) among the six investigators were 0.63, CI=[0.35-0.88] for GS synovitis, and 0.77, CI=[0.56-0.97] for PD signal respectively. Table III shows the Cicchetti weighted kappa reliability index obtained in the reading of GS images on a 4-point scale by each investigator compared to the reference investigator (PC).

Table III. Interobserver agreement in the reading of grey-scale images on a 4-point scale.

	Observers	Kappa	SE	$CI_{95\%}$ Lower-Limit	$CI_{95\%}$ Upper-Limit
GS-images US reading					
	1	**0.71**	0.08	0.54	0.87
	2	**0.56**	0.12	0.30	0.75
	3	**0.64**	0.11	0.43	0.85
	4	**0.74**	0.09	0.55	0.93
	5	**0.48**	0.08	0.30	0.56

GS: grey-scale; US: ultrasound; Kappa: level of Kappa agreement; SE: standard deviation; $CI_{95\%:}$ 95% confidence interval.

Discussion

The main objective of JIA treatment is to induce sustained disease control. Currently, several methods for detecting inactivity of disease are under the spotlight. Clinical assessment for detecting ID seems to be insufficient to ensure full biologic inactivity (6, 7, 20). Recent efforts have been carried out to identify surrogate biomarkers of disease control (21), and imaging techniques, such as US, are suitable for detecting residual synovial pathology in the case of disease persistence.

Our study provides evidence of synovitis and tenosynovitis on B-mode US in JIA patients with apparent clinical inactivity. In addition, inflammatory activity upheld by power-Doppler has been shown in a few joints from patients on medication.

Thirty-four patients with JIA were included in our study. They were clinically labelled by their clinicians as having ID after ≥6 months of follow-up prior to screening. Although the low values in the clinical assessment reported by the investigator support that those patients were in an ID state, 13 of them showed US-detected synovial pathology.

According to treatment, the patients in the IDoff group showed a longer duration of inactivity, and some of them achieved several ID states. These results are not striking considering prior literature (22, 23), as Wallace *et al*. showed that ID may be episodic, and that only 50% of children who achieve ID remained in this state for >6 months and 25% of them achieved it off medication (22).

Detection of joint space narrowing as an early destructive change in JIA during the first year of follow-up was reported in literature (11), nevertheless, this was not found in our study. Therefore, the absence of damage shown by radiography in our study did not allow comparison between imaging techniques (*i.e*. conventional radiograph and US).

US synovial pathology was detected in one-third of our patients. It was in keeping with the results reported previously (6, 7). Patients in ID on medication had a higher number of US detected findings than those in IDoff. In addition, inflammatory activity upheld by power-Doppler has been detected in a few joints of the same group. The validity of the presence of US synovial abnormalities detected in these patients is strengthened by the data of our previous study in healthy children (24).

A potential limitation that should be noted is the type of study, due to the fact that is a cross-sectional study, we are aware that to add some knowledge on the meaning of the detected subclinical synovitis in JIA is not possible. The prognostic meaning of US subclinical synovitis in JIA patients has recently been challenged by Magni-Manzoni *et al*. (6) who reported that US detected synovial abnormalities including the Doppler signal, were unable to predict a flare of synovitis in JIA patients with clinical ID. In keeping with baseline results of the same study (6), we found that most synovial pathology detected on B-mode US was scored in grade 1. Since there is a scarcity of literature focusing on the follow-up of US sub-

clinical synovitis in JIA, the interesting observation reported in the Magni-Manzoni study should be treated with caution. Recently, Witt *et al*. studied longitudinally the wrist and the small joints of the hand in rheumatoid arthritis. They reported that detected ultrasonographic changes were significantly less in joints with GS-synovitis scored as grade 1, than the others with grades 2-3 (25). Given that, it is difficult to determine whether synovitis detected solely by B-mode US represents chronic fibrotic changes or active changes (26), the presence of power-Doppler in the synovium seems to confirms active inflammation (27). According to the definition of positive PD signal used in our study, its detection let us determine that nearly half of the joints with GS-synovitis had sustained activity. It was observed particularly in the IDon group. Tenosynovitis detected on US was less and it was in agreement with prior studies (6). Interobserver reliability was moderate for GS synovitis and good for PD signal, suggesting the need to reach a consensus on scoring systems.

Although our patients were in a clinical inactivity state, US enabled the detection of synovial pathology. Thus, US should help in clinical decision-making regarding the length of JIA therapy after ID is achieved. Our data might explain, at least conceptually, why relapses are possible when medications are tapered or discontinued: ID and remission might be still a biologically abnormal state at the joint level. Furthermore, Knowlton *et al*. (28) demonstrated that ID in JIA represents a homeostatic condition in which pro-inflammatory and anti-inflammatory mechanisms appear to be in balance, but not a return to a normal state. However, from the point of view of clinical practice, long-term prospective studies are required to establish the clinical relevance US findings in children with ID, particularly on B-mode US.

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