Paediatric rheumatology

Ultrasound changes in synovial abnormalities induced by treatment in juvenile idiopathic arthritis

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Abstract

Objective

To investigate the capacity of ultrasound (US) to detect improvement of synovial abnormalities induced by treatment in juvenile idiopathic arthritis (JIA).

Methods

Eighty-three joints (33 knees, 22 tibiotalar, 10 wrists, 9 elbows, 9 subtalar joints) of 33 patients with new-onset JIA were assessed by US at study entry and 6 months after a therapeutic intervention. Each joint was scored for grey-scale (GS) and power Doppler (PD) abnormalities according to a 4-point semiquantitative scale. Pre- and post-treatment US scores were compared and the sensitivity to change of GSUS and PDUS was estimated. Clinical response was assessed using the ACR paediatric (ACRp) response criteria.

Results

Seventeen patients (51.5%) underwent intra-articular corticosteroid injection (IACI) only, 15 (45.5%) were given IACI and systemic medications, and 1 (3.0%) was started with systemic therapy alone. Both GSUS and PDUS scores improved significantly ($p<0.0001$) from baseline to follow-up. US revealed strong sensitivity to change with standardised response mean for GSUS and PDUS of 2.44 and 1.23, respectively. At the follow-up visit, 13/20 (65.0%) joints with residual US abnormalities were judged in remission on clinical grounds. Six/21 (28.6%) patients who were ACRp90 responders did not display complete resolution of synovial abnormalities on US.

Conclusion

US is a sensitive tool to assess therapeutic response in patients with JIA. Subclinical disease on US is common in joints with clinically-defined remission. An ACRp90 response may not be coupled with complete resolution of synovial abnormalities on US. Further studies are needed to establish the impact of US on therapeutic decision-making in JIA.

Key words

ultrasound, juvenile idiopathic arthritis, large joints

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Received on April 2, 2017; accepted in revised form on June 12, 2017.

Competing interests: none declared.

Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood and a leading cause of acquired disability (1). Over the last few years, the expanding application of ultrasound (US) in paediatric rheumatology settings has enabled clinicians to directly visualise synovial abnormalities of joints of patients with JIA.

US has proven to be a safe, easy, readily available, and relatively inexpensive imaging tool for the assessment of articular and periarticular structures in JIA (2). The lack of exposure to ionising radiation, the high acceptability by patients, and the ability to allow real-time and multiplane imaging of several joints in a single scanning session make this technique suitable and appealing for use in children with chronic arthritis (3, 4). These advantages may explain why US is becoming an important adjunct to clinical evaluation (5).

Several studies have documented that subclinical synovitis is frequently detected by US in children with JIA (6-8). These observations are relevant because incomplete suppression of joint inflammation may increase the risk of developing permanent structural damage (9).

Accurate monitoring of response of joint synovitis to therapy is crucial in routine practice and in clinical trials. Synovitis is generally evaluated indirectly, by assessing objective and subjective clinical signs and laboratory parameters of inflammation. Owing to its potentially greater sensitivity, US could be ideally coupled with clinical and laboratory evaluation to assess the course of joint disease activity during treatment with anti-rheumatic medications, as suggested by the recently published "points to consider" for the use of imaging in JIA in day-to-day clinical practice (10). However, although US has been shown to be valuable in monitoring treatment response in adult patients with rheumatoid arthritis (11-14), its role in children with chronic inflammatory arthritis still needs to be clarified.

The aim of the present study was to investigate the ability of US to assess treatment-induced changes in synovial abnormalities in children with new-onset JIA.

Materials and methods

Patient selection

All consecutive patients with new-onset JIA, classified according to the International League of Associations for Rheumatology (ILAR) criteria (15), who were seen between November 2013 and November 2014 at the rheumatology outpatient clinic of the Istituto G. Gaslini of Genova, Italy, underwent a bilateral US assessment of the following joints: elbows, wrists, knees, tibiotalar and subtalar joints. Patients who showed US-detected synovial abnormalities in at least one joint were considered eligible and were asked to participate in the study. A previous treatment with intra-articular corticosteroid injections (IACIs) or any systemic medication, with the exception of non-steroidal anti-inflammatory drugs, was considered as an exclusion criterion. Informed consent was obtained from all children, parents or guardians, as appropriate. The study protocol was approved by the local Institutional Review Board.

Clinical and laboratory assessment

At study visit, the following data were recorded for each patient: sex, age at disease onset and at study entry, disease duration, ILAR category, antinuclear antibody (ANA) status, erythrocyte sedimentation rate and C-reactive protein levels, physician's global assessment (PhGA) and patient's (or parent's) global assessment (PGA) of disease activity on a 10-cm visual analogue scale (VAS; where 0 = no activity and 10 = maximum activity), and the Italian version of the Childhood Health Assessment Questionnaire (CHAQ) (16). Clinical assessment was performed by two experienced paediatric rheumatologists (AR or SV). Clinically active disease in a joint was defined as the presence of swelling or, if no swelling was present, of tenderness/pain on motion and restricted motion (17). The clinical response was assessed using the American College of Rheumatology Paediatric (ACRp) response criteria (18). The "clinical" (*i.e.* 3-item), 10-joint version of the juvenile arthritis disease activity score (cJADAS-10) (19) was used to quantify clinical disease activity.

Table I. Therapeutic interventions for each type of joint.

Joint (n)	IACI only n (%)	Systemic medications only n (%)	IACI + Systemic medications n (%)
Knee (33)	19 (57.6)	4 (12.1) - 2 MTX; 2 MTX + SC	10 (30.3) - MTX
Tibiotalar (22)	4 (18.2)	2 (9.1) - MTX + SC	16 (72.7) - MTX
Subtalar (9)	1 (11.1)	2 (22.2) - MTX	6 (66.7) - MTX
Wrist (10)	0 (0.0)	2 (20.0) - MTX + SC	8 (80.0) - 6 MTX; 2 MTX + SC
Elbow (9)	2 (22.2)	3 (33.3) - 2 MTX; 1 MTX + SC	4 (44.5) - MTX

*IACI: intra-articular corticosteroid injection; MTX: methotrexate; SC: systemic corticosteroids.

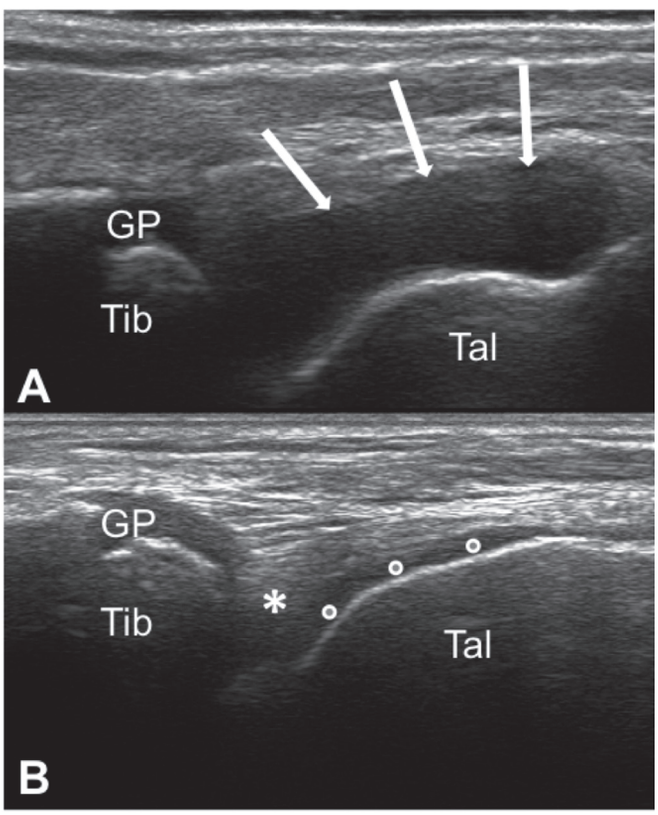

Fig. 1. Longitudinal scan of the tibiotalar joint in a 4-year-old boy with JIA. Presence of synovial abnormalities (arrows) on GSUS at baseline (**A**), and their total regression at the follow-up assessment (**B**).
GP: growth plate
Tal: talus
Tib: tibia
*: fat pad
°: articular cartilage

Ultrasound assessment

US assessment of joints was performed immediately after the clinical evaluation by a paediatric rheumatologist experienced in US assessment of patients with JIA (SL), blinded to clinical findings. Imaging was conducted using an Esaote MyLab Twice machine equipped with a multifrequency linear probe (3-13 MHz linear transducer). Images were collected using the following power Doppler (PD) settings: pulse repetition frequency (PRF) 750 Hz, low wall filter, and colour gain just below the level that did not display color noise in the underlying bone. The joints were imaged for the highest level of expression of synovial abnormalities on US using a multiplanar evaluation according to published guidelines proposed for adults (20) and were investigated on grey-scale US (GSUS) and immediately thereafter on PDUS. US abnormalities were defined according to the Outcome Measures in Rheumatology Clinical Trials (OMERACT) standardised definitions for US pathology (21). PD signal was considered positive in the presence of vessel dots inside the synovial hypertrophy (SH). Joint involvement on US was defined as the presence of both or either joint effusion (JE) and SH, which could exhibit PD signal. For the purpose of scoring, SH and JE were combined into an overall GSUS score, which was representative of the joint cavity widening. Overall GSUS and PDUS scores were graded on a 4-point semiquantitative scale based on previous studies (6, 22-24). Joint cavity widening was graded as follows: 0 = absent, 1 = mild, 2 = moderate, 3 = marked. PD signal was graded as follows: 0 = absent, 1 = mild, presence of single-vessel dots, 2 = moderate, presence of confluent vessel dots in less than half of the synovial area, 3 = marked, presence of confluent vessel dots in more than half of the synovial area.

Follow-up assessments

Both clinical and US assessments of joints with synovial abnormalities on US at study entry were repeated 6 months after the therapeutic intervention.

Reliability

In order to estimate the intra-observer reliability, stored scans of baseline and follow-up assessment of a random subgroup of 10 patients included in the study were reassessed and rescored by the same sonographer (SL) 3 months after the end of the study.

Statistical analysis

Descriptive statistics were reported in terms of medians and interquartile ranges (IQRs) for continuous variables and as absolute frequencies and percentages for categorical variables. Pre- and post-treatment GSUS and PDUS scores were compared using the Wilcoxon signed-rank test. The sensitivity to change of GSUS and PDUS scores was estimated by computing the standardised response mean (SRM), which was calculated as the ratio between the mean and the SD of the change in scores. The threshold levels for SRM were defined as follows: ≥0.20=small, ≥0.50=moderate, ≥0.80=strong (25). Intra-observer reliability was evaluated through the weighted Cohen's kappa statistics (k) (26). The strength of k 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 excellent (27).

Results

A total of 33 patients, 28 girls and 5 boys with US involvement of 83 joints (33 knees, 22 tibiotalar joints, 10

wrists, 9 elbows and 9 subtalar joints) were included in the study. At study entry, the median disease duration was 0.2 years (IQR 0.1-0.3 years), and the median age was 3.2 years (IQR 2.0-5.6 years). Twenty patients (60.6%) had oligoarthritis and 13 patients (39.4%) had polyarthritis (12 rheumatoid factor (RF)-negative and 1 RF-positive). ANAs were positive in 24 patients (72.7%), 17 with oligoarthritis and 7 with RF-negative polyarthritis.

At study entry, 17 patients (51.5%) underwent an IACI without the start of any systemic medication, 15 patients (45.5%) were given IACI and systemic medications (14 patients methotrexate alone and 1 patient methotrexate plus systemic corticosteroids), and 1 patient (3.0%) was treated with systemic corticosteroids plus methotrexate. Table I summarises the therapeutic interventions in relation to each type of joint.

At the follow-up visit, 70/83 joints (84.3%) were in clinical remission (*i.e.* showed disappearance of all clinical signs of articular inflammation), and 63/83 joints (75.9%) had resolution of all US-detected synovial abnormalities. Complete regression of all synovial abnormalities on US was observed in 17/22 (77.3%) tibiotalar joints, 25/33 (75.8%) knees, 5/9 (55.6%) subtalar joints, 8/9 (88.9%) elbows, and 8/10 (80.0%) wrists. Residual synovial abnormalities were detected by US at 6 months in 13/70 joints (18.6%) (5 knees, 3 tibiotalar joints, 2 subtalar joints, 2 wrists and 1 elbow) judged in remission on clinical examination of 11 patients. Figure 1 shows an example of complete normalisation of baseline GSUS findings at follow-up assessment.

The frequency of specific US features for each joint is reported in Table II. At baseline, JE was more commonly found in the knee. All subtalar joints and elbows had SH, which was also seen in nearly all knees (97.0%) and tibiotalar joints (95.5%). The joint with the higher rate of positivity for PD signal was the subtalar (88.9%), followed by the wrist (80.0%). At the follow-up visit, SH was the most common US feature, being recorded in 16 joints, mostly in the subtalar joint. JE was more frequently detected in the knee. PD signal was recorded only in 1 knee and in 2 subtalar joints.

Table II. Frequency of US abnormalities at baseline and follow-up assessments.

Joint (n)	Baseline n (%)			Follow-up n (%)		
	JE	SH	PD	JE	SH	PD
Knee (33)	32 (97.0)	32 (97.0)	22 (66.7)	6 (18.2)	5 (15.2)	1 (3.0)
Tibiotalar (22)	19 (86.4)	21 (95.5)	14 (63.6)	2 (9.1)	4 (18.2)	0 (0.0)
Subtalar (9)	7 (77.8)	9 (100)	8 (88.9)	1 (11.1)	4 (44.4)	2 (22.2)
Wrist (10)	6 (60.0)	9 (90.0)	8 (80.0)	0 (0.0)	2 (20.0)	0 (0.0)
Elbow (9)	7 (77.8)	9 (100)	5 (55.6)	1 (11.1)	1 (11.1)	0 (0.0)

*US: ultrasound; JE: joint effusion; SH: synovial hypertrophy; PD: power Doppler.

Table III shows the frequency of GSUS and PDUS scores at baseline and follow-up assessments in the 83 joints with synovial abnormalities on US at study entry. A decrease in GSUS score, and in PDUS score when ≥1 at baseline, was seen in 16 (80.0%) of the 20 joints which had residual US abnormalities at the follow-up evaluation. Reduced PDUS score with unchanged GSUS score was documented in 2 knees. One subtalar joint and 1 knee did not show any change in scoring on GSUS and PDUS between baseline and follow-up assessments. The GSUS and PDUS scores at baseline and follow-up assessments of the 20 joints with residual US abnormalities at follow-up is reported in Table IV.

Intra-observer reliability was excellent (k=0.96) and good (k=0.74) for assessment of GSUS and PDUS findings, respectively.

The median (IQR) GSUS score decreased from 2.0 (2.0-3.0) at baseline to 0.0 (0.0-0.0) at the follow-up visit (p<0.0001). Likewise, the median (IQR) PDUS score diminished from 2.0 (0.0-2.0) to 0.0 (0.0-0.0) (p<0.0001) between baseline and follow-up visits. The SRM values for both GSUS and PDUS scores (2.44 and 1.23, respectively) from baseline to 6 months indicated strong sensitivity to change.

The assessment of the ACRp response at the follow-up visit revealed that 21/33 patients (63.6%) were ACRp90 responders. Six (28.6%) of these patients did not display complete resolution of synovial abnormalities on US in at least one affected joint.

Seventeen (51.5%) of the 33 study patients were in clinical remission by the cJADAS-10 (*i.e.* had a cJADAS-10 value ≤1) at the follow-up visit. In 7 joints (2 knees, 2 tibiotalar joints, 2 wrists and 1 subtalar joint) of 5 patients of this group, we did find persistence of GSUS abnormalities at follow-up, but not PDUS abnormalities.

Discussion

In the last decade, several studies have emphasised the utility of applying imaging procedures, together with clinical assessment, in the management of children with chronic inflammatory arthritis. A list of points to consider for the use of imaging in JIA in day-to-day clinical practice has recently been published (10). One of these points states that US and magnetic resonance imaging can be useful in monitoring of disease activity. Imaging methods have become increasingly important after the introduction of the novel and potent biologic medications for the treatment of JIA, which have induced the need to estimate with greater precision the degree of joint synovitis. Thanks to the technological advances, which have led to the miniaturisation of US equipment, and enable the visualisation of high-level images, and to the availability of smaller, handy and higher frequency probes, US is now regarded as the most attractive imaging modality in children with JIA.

To our knowledge, our study is the first that provides data on the impact in US-detected synovial abnormalities of therapeutic intervention in children with new-onset JIA. The choice to recruit a patient sample with new-onset disease was due to our interest in studying changes over time in synovial abnormalities on US in patients "drug-naïve". We did not scan the small joints of the hands and feet to shorten the length of

Table III. Frequency of GSUS and PDUS scores at baseline and follow-up assessments in the 83 assessed joints.

Joint (n)	Baseline n								Follow-up n							
	GSUS score				PDUS score				GSUS score				PDUS score			
	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
Knee (33)	0	4	12	17	11	5	17	0	25	6	1	1	32	0	1	0
Tibiotalar (22)	0	1	12	9	8	4	10	0	17	5	0	0	22	0	0	0
Subtalar (9)	0	0	4	5	1	1	3	4	5	1	3	0	7	1	1	0
Wrist (10)	0	1	3	6	2	1	4	3	8	0	2	0	10	0	0	0
Elbow (9)	0	2	3	4	4	4	1	0	8	1	0	0	9	0	0	0

*GSUS: grey-scale ultrasound; PDUS: power Doppler ultrasound.

Table IV. GSUS and PDUS scores at baseline and follow-up assessments of the 20 joints with residual US abnormalities at follow-up.

Joint	Baseline		Follow-up	
	GSUS score	PDUS score	GSUS score	PDUS score
1- Knee	2	0	1	0
2- Knee	2	0	1	0
3- Knee	3	2	1	0
4- Knee	3	2	3	2
5- Knee	3	2	1	0
6- Knee	2	2	2	0
7- Knee	1	1	1	0
8- Knee	3	2	1	0
9- Tibiotalar	3	0	1	0
10- Tibiotalar	3	1	1	0
11- Tibiotalar	3	2	1	0
12- Tibiotalar	2	0	1	0
13- Tibiotalar	2	0	1	0
14- Subtalar	2	0	2	0
15- Subtalar	3	3	2	0
16- Subtalar	3	2	1	1
17- Subtalar	3	3	2	2
18- Wrist	3	0	2	0
19- Wrist	3	2	2	0
20- Elbow	3	2	1	0

*GSUS: grey-scale ultrasound; PDUS: power Doppler ultrasound; GSUS score range: 0-3; PDUS score range: 0-3.

the US assessment, and the hip and the shoulder because these joints are seldom affected at disease onset in JIA.

The therapeutic decision for each patient was made by the caring physician based on the overall clinical involvement and according to the personal routine practice. That nearly all joints included in the study were injected was expected, given the key role of IACI therapy in our centre (28, 29). All joint injections were performed without US guidance. Around half of the patients were simultaneously given a systemic treatment.

At the follow-up visit, the majority of joints showed disappearance of all US-detected synovial abnormalities. The main exception was represented by the subtalar joint, which showed persistent US abnormalities, in particular SH, in around half of the cases. In a previous study by *Laurell et al*. (30), which was centered on the diagnosis and follow-up of US-guided steroid injections in the ankle region, normalisation of both SH and Doppler signal was found in 95% of the subtalar joints injected using US guidance. The lower rate of regression of synovial abnormalities in the subtalar joint seen in our study may be due to the lack of use of US guidance.

We found that US is a very sensitive method to document changes in joint inflammation after the start of a therapeutic intervention. Our data indicate that such changes can be clearly seen on US, which is safe, easy and readily available, relatively inexpensive and well-tolerated among children with JIA. No other imaging modality shares all these features together. Overall, intra-observer reliability for the assessment of both GSUS and PDUS was satisfactory.

Our study confirms the previous reports of a frequent discordance between clinical and US assessments in children with JIA (6-8, 31-33). We found residual synovial abnormalities on US at 6 months in almost one fifth of joints judged in remission on clinical grounds. In addition, around one forth of patients, who experienced a major clinical improvement, as shown by the fulfillment of the ACRp90 response criteria, were found to have persistent US abnormalities in at least one joint. To further support these assumptions, we found also that a considerable portion of patients in clinical remission by the cJADAS-10 at the follow-up visit showed persistence of synovial abnormalities on US. Altogether, these findings underscore the need of performing longitudinal studies aimed to assess the predictive value of subclinical disease on US in JIA.

There are some study limitations to consider. The time interval between baseline and follow-up assessment was wide. This was mainly due to most recruited patients living far from our centre, which made frequent travels to our hospital not feasible. Therefore, we cannot exclude that we have interpreted as incomplete regression of US synovial abnormalities disease flares after pre-

vious remission of synovitis. We should also recognise that, due to the current lack of established cut-off values for GSUS and PDUS scores that discriminate between active and inactive disease in JIA, we considered the presence of any synovial abnormalities on US as a sign of subclinical disease. This choice could have led to an overestimation of disease burden. Conversely, the exclusion of small hands and feet joints and of shoulder and hip from US assessments could have led to miss some important sites of joint involvement. We finally recognise that because none of our patients was given biologics, our findings do not reflect the effectiveness of these medications.

In summary, our study suggests that US is a sensitive method to assess changes in synovial abnormalities induced by a therapeutic intervention in children with JIA. Our findings confirm the frequent presence of subclinical disease on US in joints judged in remission on clinical grounds. Residual US synovial abnormalities were also seen in a sizable proportion of patients who experienced a profound clinical improvement, as shown by the fulfillment of the ACRp90 response criteria. This discrepancy between clinical and US assessments may affect the evaluation of the outcome of therapeutic interventions and may have important implication for patient prognosis. Further studies are needed to define the role of US in monitoring treatment efficacy and to evaluate the impact of this imaging modality on therapeutic decision-making in JIA.

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