Ultrasound-detected tenosynovitis in ankles with clinical arthritis and short-term outcome of patients with new-onset juvenile idiopathic arthritis

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Abstract

Objective

To determine features and frequency of ultrasound (US)-detected tenosynovitis in ankles with clinically active disease and to investigate whether its detection may affect the achievement of inactive disease in patients with new-onset juvenile idiopathic arthritis (JIA).

Methods

The study included children with new-onset JIA and clinically active disease of the ankle. Based on US, patients were stratified as having isolated arthritis or as having tenosynovitis irrespective of the presence of concomitant arthritis in the ankle. Estimation of patients who were able to achieve clinically inactive disease 6 months after starting treatment was assessed by the Kaplan-Meier method. Cox model was used to calculate hazard ratio (HR) and 95% confidence interval (CI). Reliability of US was tested using kappa statistic.

Results

Forty-five patients were recruited. On US, tenosynovitis of the ankle was detected in 28 patients (62.2%); isolated arthritis was found in 17 patients (37.8%). The medial and lateral tendon compartments were the tendon sites most frequently inflamed. Patients with tenosynovitis had similar likelihood of those without tenosynovitis to achieve clinically inactive disease (60.7% and 58.8%, respectively; HR 1.12, 95%CI:0.51–2.45). In the subanalysis excluding patients who were given biologics, the probability of experiencing inactive disease was slightly higher for patients with tenosynovitis compared to those without (64.7% and 54.5%, respectively; HR 1.56, 95%CI: 0.58–4.24). The rate of US reliability was high.

Conclusion

US-detected tenosynovitis is frequent in ankles with clinical arthritis at JIA onset but does not impair the chance of achieving clinically inactive disease in the early disease phase.

Key words

juvenile idiopathic arthritis, ultrasound, tenosynovitis

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic joint disease in paediatric rheumatology and may result in structural damage and, consequently, inability in childhood when not timely and effectively treated (1).

It is well-known that the ankle is one of the more frequently affected sites throughout the disease course. This joint is also regarded as a potential hallmark of detrimental outcome (2). Accurate assessment of the ankle in JIA is therefore crucial in order to rule out any sign of inflammation in joints and tendons in terms of synovitis and tenosynovitis, respectively.

Coupling clinical assessment with imaging modalities, such as ultrasound (US), in the ankle region has been reported to increase significantly the capacity to identify precisely the exact location of inflammation in children with JIA (3-7). The reason for which US is preferred to other imaging techniques in the paediatric rheumatology clinical setting is explained, at least in part, by the fact that it is very well tolerated by children, can be performed at the bedside, does not entail exposition to ionising radiation, and allows to study several sites in the same session (8-12). Despite all these advantages, the precise role of US in the management of patients with JIA is yet to be fully defined. In particular, there is a current lack of knowledge on the predictive significance of US findings in JIA, since the small body of data that has been published on this topic so far leads to clearly conflicting results (13-20).

Taking into account that inflammation in JIA can be located not only in the joint recesses, but also at the level of tendon sheaths, especially in the ankle, and that discrimination between articular and tendon swelling is challenging with clinical assessment alone, it would be advisable to understand whether the detection of tenosynovitis on US may identify a subset of patients with a different burden of disease compared to patients without tenosynovitis.

Of interest, in a recent study on a population of patients with rheumatoid arthritis (RA) in clinical remission US-detected tenosynovitis of the hand and wrist joints, that are common targets of RA, has been seen to predict unstable disease remission (21).

Given the fact that, unlike adults with RA, the ankle is the site where tenosynovitis is by far more commonly detectable on US in children with JIA compared to the wrist (22), this anatomic region may be considered as a "target joint" to study the prognostic meaning of tenosynovitis in JIA. In this context, in addition to the information on the predictive utility of US findings in patients with clinical disease remission, it is appropriate to investigate also the prognostic meaning of US-detected tenosynovitis in patients with new-onset JIA and clinical involvement of the ankle region. In fact, unravelling this topic could lead to important implications in clinical practice, such as the introduction of tailor-made therapies for patients early in the disease course, with the final goal to improve the outcome of JIA.

Against this background, the aim of our pilot study was therefore twofold: 1) to determine features and frequency of US-detected tenosynovitis in patients with new-onset JIA and clinically active disease of the ankle region; 2) to investigate whether the detection of tenosynovitis on US in the ankle region at JIA onset may affect the achievement of a state of inactive disease of patients after starting a therapeutic intervention according to standard-of-care practice.

Materials and methods

Patient selection

The study included retrospectively consecutive children with new-onset JIA, classified according to the International League of Associations for Rheumatology (ILAR) criteria (23), who had clinically active disease in the ankle region and underwent US assessment of the ankle, and who were evaluated for the first time between January 2020 and December 2021. The patients were recruited from the Paediatric Rheumatology Associated Group of the Milan Area (PRAGMA) centres (the Paediatric Immunorheumatology Unit of the Istituto di Ricovero e Cura a Carattere Scientifico Ospedale Maggiore Policlinico of Milan, Italy, and

the Paediatric Rheumatology Unit of the Gaetano Pini Institute of Milan, Italy). A documented follow-up of at least 6 months from the first therapeutic intervention was regarded as mandatory for considering a patient eligible for the study. Informed consent was obtained from all children, parents or guardians, as appropriate. The study protocol was approved by the local Institutional Review Board of the Milan Area.

Baseline and follow-up clinical assessment

At enrolment, the following baseline data were retrieved from the clinical charts and recorded for each patient: sex, age at disease onset and at JIA diagnosis, disease duration, number of affected joints at disease onset, antinuclear antibody (ANA) status, ILAR category, therapy received in the first 6 months from JIA diagnosis. Clinically active disease affecting the ankle was defined as the presence of swelling or, if no swelling was present, of tenderness/pain on motion and restricted motion of the ankle region (24). Follow-up clinical data were collected again through clinical chart review to assess achievement of inactive disease according to published criteria (25).

US assessment

Data concerning US assessments were retrieved from images of patients stored in the US equipments. As per routine practice in the enrolling centres, the US exam was performed after clinical assessment of the ankle region, with the aim to confirm active disease and, then, to precisely identify the exact location of inflammation. All US evaluations were performed by paediatric rheumatologists experienced in US assessment of patients with JIA (SL and ODL). Imaging was conducted using an Esaote MyLab Alpha machine (SL) or an Esaote MyLab 70 machine (ODL), both equipped with a multifrequency linear probe (3–13 MHz and 6–18 MHz linear transducers, respectively). The settings of the US machines were calibrated for the assessment of joints and tendons of children with chronic inflammatory arthritis. US examinations were performed based upon standard EULAR reference scans (26) and US findings were interpreted according to the OMERACT definitions of pathology (27). Synovitis on US of the ankle region was defined as the presence of both or either joint effusion and synovial hypertrophy in at least one of the following sites: tibiotalar joint (TTJ), subtalar joint (STJ) and intertarsal joint (ITJ) (talo-navicular and navicular-1st cuneiform joints assessed together). Ultrasound-detected tenosynovitis of the ankle region was defined as the presence of hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath, which is seen in two perpendicular planes and which may exhibit power Doppler (PD) signal, in at least one of the tendons of the following tendon compartments: the anterior tendon compartment (ATC) (tibialis anterior, extensor hallucis longus, extensor digitorum longus), the medial tendon compartment (MTC) (tibialis posterior, flexor digitorum longus, flexor hallucis longus) and the lateral tendon compartment (LTC) (peroneus longus and brevis) of the ankle. Each US abnormality was simply recorded as present/absent.

Outcome assessment

Based on US findings of the ankle region, patients were stratified in the following two groups: 1) patients with detection of isolated arthritis (synovitis) affecting at least one of the joints of the ankle; 2) patients with detection of tenosynovitis involving at least one of the tendon compartments of the ankle irrespective of the presence of concomitant arthritis. For the purpose of the analysis, in case of involvement of both ankles in a patient, US findings were combined altogether in order to define the patient as having or not having tenosynovitis of the ankle region. In the two groups, estimation of patients who were able to achieve a state of clinically inactive disease according to the Wallace criteria (25) was assessed after 6 months from the first therapeutic intervention.

Reliability

Intra- and inter-observer reliability of US was assessed on still images. Stored scans of all patients included in the study were reassessed by both the sonographers who performed US examinations after 3 months from the first evaluation. Any discrepancies on US findings were then resolved through a discussion between the sonographers before data analysis.

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. Mann-Whitney U-test was used to analyse quantitative variables, whereas comparison of qualitative data was performed by means of the chi-square test, or by Fisher's exact test in the case of expected frequencies <5. Agreement was estimated through the unweighted Cohen's kappa statistics (k) with 95% confidence intervals (CI) (28). 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 (29). Achievement of clinically inactive disease in each group was evaluated with Kaplan-Meier method and by calculating hazard ratio (HR) and CI using Cox model. Survival curves were compared by the log-rank test. Statistical analyses were performed with Stata 17 (StataCorp. 2021).

Results

Study population

A total of 45 patients, 29 girls (64.4%) and 16 boys (35.6%), with new-onset JIA and clinically active disease of the ankle region were included in the study. Fourteen patients (31.1%) had persistent oligoarthritis, 4 (8.9%) had extended oligoarthritis, 23 (51.1%) had rheumatoid factor (RF)-negative polyarthritis, and 4 (8.9%) had enthesitis-related arthritis. ANAs were positive in 29 patients (64.4%). At first evaluation in the study centres, the median disease duration was 0.2 years (IQR 0.1–0.3 years), and the median age was 5.5 years (IQR 3.2–9.2 years). The median number of joints affected at disease onset was 5.0 (3.0–8.0). Seventeen patients had clinically active disease of both ankles. Forty-three pa-

tients (95.6%) started methotrexate at the time of diagnosis; 17 of them added subsequently anti-tumour necrosis factor (TNF) agents in the first 6 months from the diagnosis of JIA. Two patients (4.4%) underwent injections in the ankle region alone. Table I shows the clinical features of patients according to the presence or absence of tenosynovitis on US of the ankle region. Patients with US-detected tenosynovitis were younger, were more frequently females, and had more commonly positive ANAs. A polyarticular course was the most frequent subtype of JIA irrespective of the presence of tenosynovitis of the ankle. Overall**,** number of joints affected at disease onset and disease duration at diagnosis of JIA were comparable in the two groups of patients. Comparing patients for treatment, slightly more than one third of patients belonging to each group received a biologic agent during the 6 months of follow-up. The 2 patients who underwent joint injections only did not have tenosynovitis of the ankle region.

Table I. Clinical features of patients according to the presence or absence of tenosynovitis on US of the ankle region.

Feature	Tenosynovitis yes (n=28)	Tenosynovitis no (n=17)	*p*-value
Gender: female	20 (71.4%)	9 (52.9%)	0.21
Age at disease onset, median (IQR), years	4.4 (2.7-9.0)	6.6 (4.2-8.5)	0.25
Age at JIA diagnosis, median (IQR), years	4.6 (2.9-9.2)	7.0 (4.6-8.6)	0.30
Disease duration, median (IQR), years	0.2 (0.1-0.2)	0.3 (0.1-0.3)	0.54
Joints affected at disease onset, median (IQR)	5.0 (3.0-7.0)	4.0 (3.0-14.0)	0.86
Patients with positive ANA	20 (71.4%)	9 (52.9%)	0.21
ILAR category			0.19
Persistent oligoarthritis	9 (32.1%)	5 (29.4%)	
Extended oligoarthritis	4 (14.3%)	0 (0.0%)	
RF-negative polyarthritis	14 (50.0%)	9 (52.9%)	
Enthesitis-related arthritis	1 (3.6%)	3 (17.6%)	
Therapy received in the first 6 months from JIA diagnosis			
Local injection therapy	28 (100%)	13 (76.5%)	0.02
Methotrexate	28 (100%)	15 (88.2%)	0.14
Biologic agents	11 (39.3%)	6 (35.3%)	0.78

Data are represented as n (%), unless otherwise indicated.
ANA: antinuclear antibody; JIA: juvenile idiopathic arthritis; ILAR: International League of Associations for Rheumatology; RF: rheumatoid factor.

Table II. US features of the 17 patients with bilateral involvement of the ankle region with particular focus on the tendon compartments affected by tenosynovitis.

Patient	Right ankle	Left ankle	Overall ankle tenosynovitis*
1	synovitis	synovitis	No
2	synovitis + ATC, MTC, LTC	synovitis + ATC, MTC, LTC	Yes
3	synovitis	synovitis	No
4	synovitis	synovitis + LTC	Yes
5	synovitis + MTC	synovitis + MTC	Yes
6	synovitis	synovitis	No
7	synovitis	synovitis	No
8	ATC + LTC	ATC + LTC	Yes
9	synovitis + ATC, MTC, LTC	synovitis + ATC, MTC, LTC	Yes
10	synovitis + ATC, MTC	synovitis	Yes
11	synovitis	synovitis	No
12	synovitis+ MTC, LTC	synovitis + MTC, LTC	Yes
13	synovitis + ATC, MTC	synovitis + MTC, LTC	Yes
14	synovitis	synovitis	No
15	synovitis + MTC, LTC	synovitis	Yes
16	synovitis	synovitis	No
17	synovitis + MTC, LTC	synovitis + MTC	Yes

ATC: anterior tendon compartment; MTC: medial tendon compartment; LTC: lateral tendon compartment; synovitis refers to the presence of both or either joint effusion and synovial hypertrophy in at least one joint among the tibiotalar joint, the subtalar joint and intertarsal joint (talo-navicular and navicular-1st cuneiform joints assessed together).
*Overall ankle tenosynoivitis refers to US features of left and right ankle combined in order to stratify the patient as having or not having tenosynovitis.

US findings of tenosynovitis

Table II illustrates the US features of the 17 patients with bilateral involvement of the ankle region. Seven of them (41.2%) did not show tenosynovitis on US in any of the two ankles. Of the remaining 10 patients with bilateral ankle clinical arthritis, 7 had US-detected tenosynovitis in both ankles, whereas 3 patients displayed tenosynovitis on US in only one of their ankles.

Overall, tenosynovitis of the ankle region was detected on US in 28 patients (62.2%). In 26 of them (92.9%), tenosynovitis was coupled with joint arthritis on US in at least one of the articular recesses of the ankle region (TT, ST, ITJ). Absence of US-detected tenosynovitis of the ankle region (*i.e.* isolated arthritis) was found in all the remaining 17 patients (37.8%).

Table III shows the frequency of US-determined tenosynovitis in the study patients according to the involvement of the different tendon compartments of the ankle region. Overall, the LTC and the MTC were the most frequently affected tendon compartments at disease onset. The number of patients with concomitant US involvement of the ATC and the MTC was equal to that of patients with concomitant involvement of the ATC and the LTC (1 patient in both cases). At disease onset, one fourth of patients displayed on US tenosynovitis affecting the MTC together with the LTC. Three patients had the ATC, MTC and LTC simultaneously inflamed. Figure 1 shows an example of tenosynovitis on US in the ankle region.

Analysis of outcome

The survival analysis by presence or absence of US-detected tenosynovitis in the ankle region, with achievement of clinically inactive disease as event of interest, is presented in Figures 2 and 3. In the survival analysis including the

Table III. Frequency of tenosynovitis on US in the 45 assessed patients*.

Tendon compartment	Patients n (%)
ATC[a]	6 (13.3%)
MTC[b]	20 (44.4%)
LTC[c]	22 (48.8%)
ATC + MTC	1 (2.2%)
ATC + LTC	1 (2.2%)
MTC + LTC	12 (26.7%)
ATC + MTC + LTC	3 (6.7%)

*In patients with clinically active disease affecting both their ankles, detection of tenosynovitis on US in the same tendon compartment of the two ankles led to classify the patient as having tenosynovitis in that specific tendon compartment of the ankle.
ATC: anterior tendon compartment; MTC: medial tendon compartment; LTC: lateral tendon compartment.
[a] Patients with tenosynovitis of the ATC irrespective of the concomitant inflammation of the MTC and/or LTC.
[b] Patients with tenosynovitis of the MTC irrespective of the concomitant inflammation of the ATC and/or LTC.
[c] Patients with tenosynovitis of the LTC irrespective of the concomitant inflammation of the ATC and/or MTC.

entire sample of patients the cumulative probability of achieving clinically inactive disease at 6-month follow-up was comparable in the two groups of patients: 17 of the 28 patients (60.7%) who had, and 10 of 17 patients (58.8%) who did not have, respectively, tenosynovitis of the ankle region on US exam were able to attain inactive disease (HR 1.12, 95% CI: 0.51–2.45). Looking at the slope of the curve, it appears that the cumulative probability of achieving inactive disease increases steadily overtime for both groups of patients. However, patients with US-detected tenosynovitis in the ankle region tended to reach inactive disease more precociously than patients without tenosynovitis on US of the ankle. The subanalysis including only patients who did not receive a biologic agent in their first 6 months of treatment for JIA showed that the cumulative probability of achieving clinically inactive disease was slightly higher for patients with tenosynovitis compared to those without tendon involvement: 11/17 (64.7%) and 6/11 (54.5%) patients, respectively (HR 1.56, 95% CI: 0.58–4.24). In agreement with the previous analysis, patients with tenosynovitis were able to attain inactive disease more

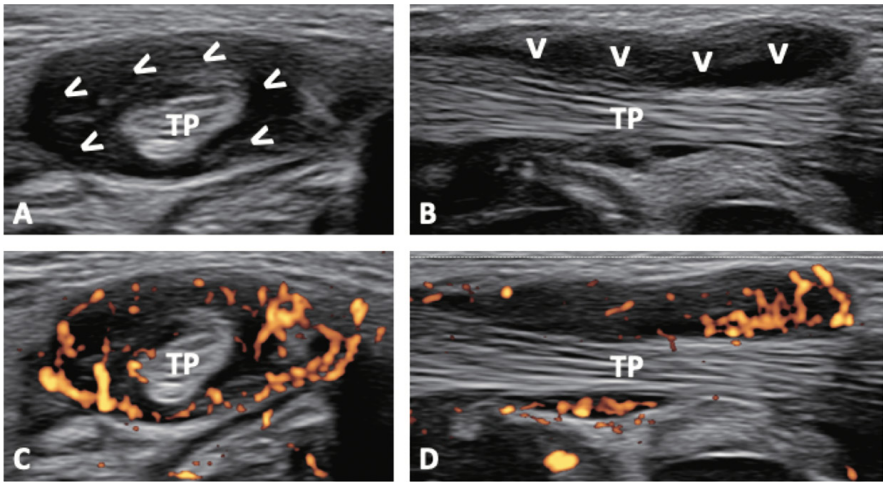

Fig. 1. Transverse (**A**, **C**) and longitudinal (**B**, **D**) ultrasound (US) scan of the tibialis posterior tendon in a 7-year-old boy with JIA showing tenosynovitis on grey scale US (**A**, **B**) and power Doppler US (**C**, **D**). TP: tibialis posterior tendon; arrowheads: distension of the tendon sheath.

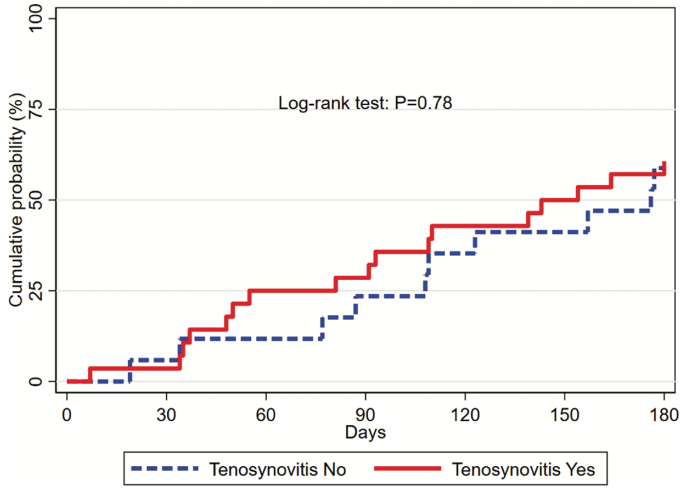

Fig. 2. Cumulative probability of achieving clinically inactive disease by presence or absence of tenosynovitis in the ankle region (Kaplan-Meier method). The analysis refers to the entire study population of 45 patients irrespective of the systemic treatment received in the first 6 months from JIA diagnosis.

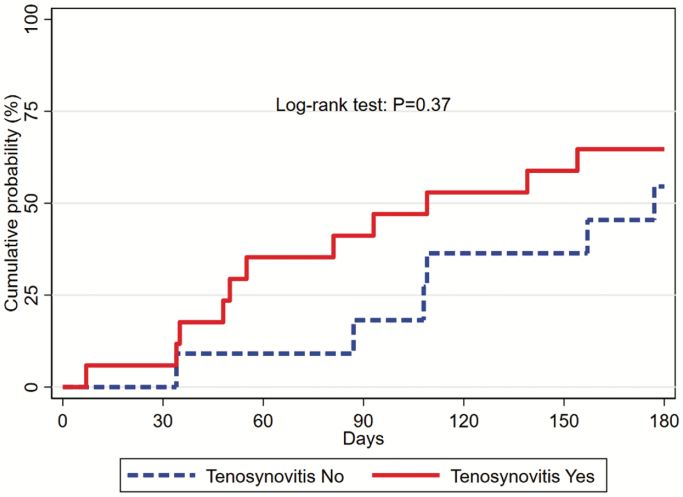

Fig. 3. Cumulative probability of achieving clinically inactive disease by presence or absence of tenosynovitis in the ankle region (Kaplan-Meier method). The analysis refers to the subgroup of 28 patients who did not receive a biologic agent (anti-tumour necrosis factor) in the first 6 months from JIA diagnosis.

precociously than the group of patients without US-detected tendon inflammation in the ankle.

Reliability of US

Intra-observer agreement for the presence of US-determined tenosynovitis *versus* isolated arthritis of the ankle region on US was excellent for both the sonographers (k=1.00, 95%CI:1.00–1.00, and k=0.95, 95%CI:0.87–1.00, respectively). Inter-observer agreement for the presence of tenosynovitis *versus* isolated arthritis of the ankle region on US was good (k=0.63, 95%CI:0.42–0.85).

Discussion

Over the last few years US has gained an increasing application among paediatric rheumatologists as a complementary tool to clinical evaluation for the assessment of patients with JIA (11-12). Among the joints that are common targets of the disease, the ankle is frequently affected and may particularly benefit from the US exam (3-7). This region is anatomically complex owing to several tendons running adjacent to the joints that are part of the ankle. Both joints and tendons may become inflamed in JIA. Accurate identification of the exact location of inflammation in the ankle is challenging in JIA by physical examination alone, because of the physiological abundant fat, the difficulty to clearly perceive the bony landmarks and the small size of the anatomical structures in children (8). Hence, correct discrimination between joint and tendon disease often requires the use of imaging modalities, such as US. Consequently, an US assessment prior to local injection therapy, especially in the ankle region, can help physician to choose precisely the sites to inject and, in turn, improves potentially the efficacy of corticosteroid injections (30).

Despite the aforementioned advantages that foster the use of US in the daily management of patients with JIA, the predictive significance of US findings in joints and tendons is an important aspect of this imaging technique that still needs to be clarified. Until now only a few studies have been conducted to investigate the prognostic role of US-detected abnormalities in JIA. Overall, these investigations were devised to explore the predictive significance of joint synovitis mainly, and led to conflicting results (13-20).

Although the current ILAR classification for JIA defines joint involvement based on the presence of active arthritis and does not take into consideration tendon inflammation (23), tenosynovitis is a well-recognised peri-articular manifestation in JIA. As such, we designed the present pilot study with the aim, first, to evaluate its prevalence at disease onset, and then, to explore whether inflammation affecting the tendon sheath in the earliest disease phase may play a key role by identifying a subset of patients with a different burden of disease compared to patients without US-detected tenosynovitis.

Unlike the previous published prognostic reports in JIA (13-20), we were interested in investigating the predictive meaning of US findings in patients with overt clinically active disease. In particular, our aim was to determine whether tenosynovitis could affect the capacity of patients to reach a state of inactive disease after starting treatment according to standard-of-care practice. To the best of our knowledge this is the first study that investigates the role of tenosynovitis in patients with clinically active JIA.

To pursue our goal, we recruited a sample of patients with new-onset JIA and clinical ankle involvement. The choice to include patients with ankle disease in our study is due to the fact that this anatomical region is by far the site where tenosynovitis is more commonly detectable on US in JIA compared to other joints surrounded by tendons, such as the wrist, which is *vice versa* a common target of RA (21). We considered, therefore, the ankle region as a "target joint" to study the prognostic meaning of tenosynovitis in JIA. This assumption is in line with the notion that the ankle is the joint where typically and more frequently tendon compartments are injected under US-guidance in JIA (22).

Our findings indicate that tendon involvement is common in patients with ankle arthritis, even at JIA onset. In keeping with the results of a previous study from our group (7), we found that US-detected tenosynovitis is more frequent in the MTC and LTC than in the ATC. As expected, a sizeable part of patients had tendon inflammation affecting simultaneously several tendon compartments of their ankles. Overall, these findings confirm the need to couple US to clinical evaluation in JIA for the assessment of anatomically complex joints, such as the ankle region, where enlargement of tendon sheaths due to inflammation may mimic joint disease.

We examined the outcome of the disease after the first 6 months of treatment for JIA according to standard-of-care practice. Our patients had, on average, early disease, as shown by the median disease duration of 0.2 years. Nearly all patients were given methotrexate; slightly more than one third of them started subsequently anti-TNF agents to achieve full control of the disease. This finding is somehow expected, since ankle arthritis often requires a second-line therapy to pursue remission in patients with JIA (2). On the survival analysis, we found that patients with tenosynovitis of the ankle region had the same likelihood of those without tenosynovitis to reach a state of clinically inactive disease at 6 months from JIA diagnosis. Similarly, the subanalysis excluding patients who were given biologics showed that the cumulative probability of achieving clinically inactive disease was even slightly higher for the group of patients with tenosynovitis compared to children without tendon inflammation on US. In addition, we found that patients with tenosynovitis tended to attain inactive disease more precociously than patients without US-detected tendon inflammation in the ankle. Taken together, these observations suggest that detection on US of tenosynovitis in ankles with clinical evidence of arthritis does not impair the chance to achieve clinically inactive disease in the early phase of JIA after starting treatment.

Our findings should be interpreted in consideration of certain potential limitations, primarily its retrospective nature. A retrospective analysis is po-

tentially subject to missing and possibly erroneous data. Second, given the multicentre design of the study, there is a risk of differences in the US evaluations and, consequently, of inaccurate interpretation of US data collection. In order to overcome this drawback, intra- and inter-observer reliability were tested on still images by the two sonographers who performed the US exams and showed in both cases a high reliability rate. In addition, to further reduce this potential risk of bias, data analysis was performed once the two operators reached consensus on discrepancies of US findings. We acknowledge also that tenosynovitis was simply recorded as present/absent irrespective of detecting PD signal within the tenosynovial sheath. Therefore, we cannot exclude that analysis including exclusively patients with PD tenosynovitis may lead to different results. Furthermore, the fact that we studied the role of tenosynovitis in patients at disease onset precludes to generalise our findings to patients with longstanding disease. Finally, in our study tenosynovitis was interpreted according to the OMERACT definitions of pathology developed for adults (27). However, this is not firmly in contrast with the recent study of the paediatric subgroup of the OMERACT US Task Force on tenosynovitis in children which demonstrated that the definition of tenosynovitis used in adults is applicable in children with only minimal modifications (31).

In summary, we found that tenosynovitis is a common finding on US at JIA onset in ankles with evidence of clinically active disease, particularly in the MTC and in the LTC. The data from our retrospective pilot study suggest that US-detected tenosynovitis in clinically active ankles does not jeopardise the chance to achieve clinically inactive disease in the early phase of JIA after starting treatment, compared to patients without tendon inflammation. Further prospective and larger studies are recommended to confirm our results.

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