Sonologic enthesitis in children with enthesitis-related arthritis

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Abstract

Objective

Enthesitis is an important clinical manifestation and is a diagnostic criterion for juvenile idiopathic enthesitis-related arthritis (JIA-ERA). Ultrasound (US) is a highly sensitive method of detection of enthesitis in adult spondyloarthropathies. However, since the data on JIA and the preformance of US compared to clinical examination is limited, we aimed to compare the accuracy of US and clinical examination in JIA-ERA.

Methods

Patients with JIA-ERA (ILAR criteria) were enrolled in the study after consent. Besides data on disease variables, enthesitis was evaluated clinically as well as by ultrasound. Six entheseal sites (iliac crest, superior pole patella, inferior pole patella, tibial tuberosity, tendoachilles and plantar fascia) on both sides of the body were examined in each patient. Features of acute and chronic enthesitis were noted.

Results

360 entheseal sites in 30 male patients (26 positive for HLA-B27), with a median age of 16 years and median disease duration of 4 years were evaluated. Median Madrid Sonology Enthesitis Index (MSEI) was 2.0 (MSEI-Acute) (IQR 0-3) and 1.0 (MSEI-Chronic) (IQR 0-1). Ultrasound enthesitis was seen in 25 of 30 patients whereas clinical enthesitis was present in 15 patients only. USG picked up 20 (47 vs. 27) more sites of enthesitis as compared to clinical examination. The concordance rate was 89.4%. Discordance was more at tibial tuberosity, superior pole patella and tendoachilles entheses.

Conclusion

Ultrasonography detects subclinical enthesitis in a proportion of patients with JIA-ERA. It can be a useful, cost-effective and safe diagnostic tool in the workup of JIA patients.

Key words

ultrasound, juvenile idiopathic arthritis, enthesitis, subclinical

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Introduction

Enthesitis refers to inflammation at the attachments of ligaments, tendons and joint capsules to the bone. The presence of enthesitis is of crucial diagnostic value in children with arthritis, since the current International League of Associations for Rheumatology (ILAR) criteria for juvenile idiopathic arthritis (JIA) classifies children with arthritis as enthesitis-related arthritis (ERA) if they have associated enthesitis (1). However the criteria consider the presence of enthesitis based on clinical examination. A few studies previously have shown that clinical examination has poor sensitivity and specificity for the detection of active and/or chronic enthesitis (2, 3). These studies found very low prevalence of enthesitis in children with JIA which was related to the fact that they had small numbers of patients with ERA, where one would expect to find large numbers of entheseal sites with inflammation. A recent study included ERA patients only and found that dolorimetric examination fared poorly in detection of enthesitis (4). Presence of entheseal site pain in some healthy children in the absence of inflammatory enthesitis also adds to the complexity of interpretation of clinical findings (5).

Recently, and mostly in adult spondyloarthropathy patients, imaging modalities like magnetic resonance imaging (MRI) and high-frequency ultrasonography (USG) have been shown to be highly sensitive and specific in the detection of enthesitis (6, 7, 17, 18). Few studies have attempted to apply these modalities in paediatric patients. Two such studies used US in JIA patients and found that ultrasound was highly sensitive in detection of enthesitis in children (2, 4). However, studies specific to ERA patients and information regarding the performance of US when compared to clinical examination in enthesitis detection are sparse.

In this study, we evaluated the presence of enthesitis and its distribution at 6 sites bilaterally in ERA patients using physical examination and ultrasonography and sought to assess the accuracy of clinical examination vis-à-vis US in the detection of enthesitis.

Patients and methods

Study subjects

Thirty consecutive new patients visiting our outpatient clinic during the period of September 2012 to September 2013, with a clinical diagnosis of JIA-ERA were enrolled into the study. The diagnosis of ERA was made by the examining physician in the outpatient clinic, as per the ILAR criteria (1). Ten healthy children, who belonged to similar socio-economic stratum, race and physical activity group as the study subjects, were also chosen from the community. The healthy controls were not related to the patients. Healthy subjects were also enrolled during the same time window as patients. The study was approved by the Institutional ethics committee and informed written consent was taken from the children and their parents or legal guardian.

Data collection

In addition to demographic features such as age and sex, disease-related information suach as disease duration, current activity, medications, HLA-B27, rheumatoid factor status and inflammatory parameters were noted for each patient. Each patient then underwent ultrasound examination on an ultrasound machine (Esaote MyLab40) equipped with high frequency (10-18 MHz linear array) transducer. All examinations were performed by the same examiner (SS) who was blinded to the clinical details. Grey scale and colour Doppler evaluations were conducted at the following six entheseal sites bilaterally in each patient: gluteus medius insertion at iliac crest (3), quadriceps tendon insertion at superior pole of patella, superior patellar tendon insertion at the inferior pole of patella, inferior patellar tendon insertion at the anterior tibial tuberosity, Achilles tendon insertion at the calcaneum and plantar fascia insertion at the calcaneum (8). Grey scale and Doppler settings were standardised for entheseal examination with pulse repetition frequency of 0.5 MHz and gain set optimally till disappearance of background noise (6, 11, 12). Two or more spots of Doppler signal were taken as significant (13). Presence of enthesitis was defined as being acute and /

Table I. Demographic and disease parameters of the study subjects.

	ERA patients (n=30)
Age at visit, median (IQR) years	16 (15–18)
Age at disease onset, median (IQR) years	12 (10–14)
Disease duration, median (IQR) years	4 (2–5)
Criteria for ERA diagnosis, no. (%)	
Enthesitis	21 (70)
Arthritis	30 (100)
Inflammatory back pain	21 (70)
Uveitis	6 (20)
Onset at age ≥6 years	30 (100)
HLA-B27 positive	26 (87)
Family history of AS, ERA, IBD with associated sacroiliitis, acute uveitis, or ReA in a first- degree relative	5 (17)
Tender joint count, median (IQR)	2 (0–4)
Swollen joint count, median (IQR)	1 (0–2)
ESR, mean (S.D) mm/ 1sthr	58.1 (31.4)
Sacroiliitis on x-ray, no (%)	9 (30)

ERA: enthesitis-related arthritis; IQR: interquartile range; AS: ankylosing spondylitis; IBD: inflammatory bowel disease; ReA: reactive arthritis.

or chronic and the Madrid Sonographic Entheseal Index (MSEI) score was calculated for each patient (8, 14). MSEI entails evaluation of five sites including quadriceps tendon insertion at superior pole of patella, superior patellar tendon insertion at the inferior pole of patella, inferior patellar tendon insertion at the anterior tibial tuberosity, tendoachilles insertion at the calcaneum and plantar fascia insertion at the calcaneum for features of acute enthesitis (thickening of tendon, hypoechogenecity of tendon, peritendinous oedema and bursitis) and chronic enthesitis (tendon tear, loss of thickness, tendon calcification and bone erosion). Each variable is scored as 0 (absence) or 1 (presence) and the MSEI is the total sum of MSEI-Acute and MSEI-Chronic. The maximum SEI scoring is 76 points (36+40). Bursitis is not assessed at inferior pole of patella and plantar fascia insertion.

Measurements of tendon thickness were taken using US calipers at sites just proximal to the commencement of the entheseal insertion. Each entheseal site was examined with the patient lying in standard positions: lateral supine position for iliac crest, supine position with knee in 30 degree flexion for superior and inferior pole of patella and tibial tuberosity, prone position with feet hanging freely at the edge of the for tendoachilles and plantar fascia (9, 10). The complete ultrasound examination of each patient took an average of 45 minutes.

After the US examination, on the same day, the children were examined by another clinician who was blinded to the clinical and ultrasound details. Clinical enthesitis was defined as the presence of pain and/or tenderness on examination at the above mentioned sites. HLA-B27 status was determined by polymerase chain reaction method. Radiographic sacroiliitis was determined on antero-posterior views of pelvis. Erythrocyte sedimentation rate (ESR) was determined by the Westergren method.

Results

All subjects were boys. The median age in healthy children was 12 years (IQR 10–14) whereas it was 16 years in children with ERA (Table I). The median age at disease onset was 12 years (IQR 10–14). 11 patients were on DMARD therapy: 7 on methotrexate and 4 on sulfasalazine and the rest were only on NSAIDs. No patients was receiving biological therapy.

Ultrasound findings

• *Control subjects*

The tendon appearance was normal in all control subjects at all examined sites in both grey-scale and colour Doppler modes.

• *ERA subjects*

Eighty three percent of the patients with ERA (25 of 30) had abnormal US findings at one or more entheseal sites, and 40% of them (12 of 30) had abnormalities at 2 or more entheses. Of the 360 entheseal site studied among 30 ERA patients, 47 sites (13%) showed features of acute and/or chronic changes.

Fifty-three percent (25 of 47 sites with US changes) had acute changes only, 13% (6 of 47 sites) had chronic changes only and 34% (16 of 47 sites) had features chronicity associated with active acute lesions. The US features seen included tendon thickening, abnormal hypoechogenicity of the tendon, peritendinous edema, bursitis, Doppler signal, intra-tendinous calcification and bony erosions. We did not observe any tendon tears or loss of tendon thickness. (Fig. 1).

The most frequent affected site was the patellar tendon insertion at the tibial tuberosity (23% [14 of 60 sites]) followed by tendoachilles entheses (21% [13 of 60 sites]), quadriceps insertion (13% [8 of 60 sites]) and plantar fascia insertion (12% [7 of 60 sites]). Abnormalities seen at each site have been described in Table II. The median MSEI-A score was 2.0 (IQR 0–3), median MSEI-C score was 1.0 (IQR 0–1) and the median total MSEI score was 2.0 (IQR 1–5).

Comparison with clinical examination

Ultrasound enthesitis was seen in 25 of 30 patients whereas clinical enthesitis was seen in 15 of 30 patients only. Hence, US examination detected 10 more patients with enthesitis than clinical examination alone. Of the total 360 entheseal sites examined US examination picked up signs of enthesitis at 29 more sites than physical examination alone. Of the 27 sites with clinical enthesitis, ultrasound enthesitis was seen in 22 sites. The overall concordance between the two methods was 333/360 sites examined (89.4%). Concordance was lowest at the tibial tuberosity (83.3%) and the tendoachilles (85%). Clinical tenderness without ultrasound evidence of enthesitis was commonly seen at plantar fascia insertion and tendoachilles entheses.

Discussion

In our cohort of 30 patients with active JIA-ERA, 22 patients had ultrasound enthesitis compared to only 15 having

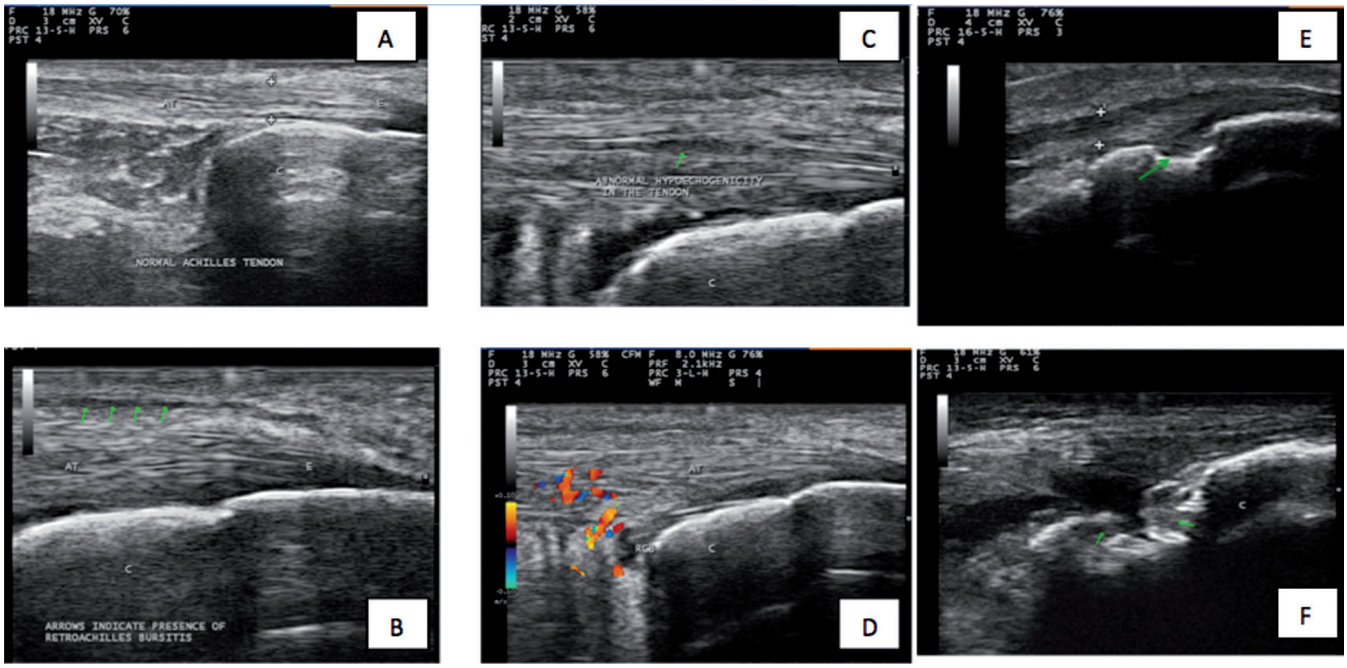

Fig. 1. Acute and chronic entheseal changes seen on ultrasound in ERA patients.
A. Grey-scale appearance of normal Achilles tendon. Cross-hairs denote ultrasound calipers used for measurement of tendon thickness. **B.** Achilles tendon demonstrating retroachilles bursitis. **C.** Achilles tendon showing increased thickness and abnormal tendon hypoechogenicity. **D.** Doppler signal seen in a case of active tendoachilles enthesitis. **E.** Bony erosion seen in calcaneum suggestive of chronic tendoachilles enthesitis. **F.** Increased fluid in retrocalcaneal bursa alongside bone erosions of calcaneum. The bone erosions were confirmed by detection on two different perpendicular planes.
AT: Achilles tendon; E: enthesitis; C: calcaneum; RCB: retrocalcaneal bursa.

clinical enthesitis. Of 360 entheseal sites, 13% sites had US features of enthesitis with majority showing active inflammation. Most common affected site was patellar tendon insertion at the tibial tuberosity. The overall concordance between ultrasound and clinical examination was 89.4% with lower concordance rates at the tibial tuberosity, Achilles tendon insertion and plantar fascia insertion.

Our prevalence of enthesitis of 13% among the sites examined by US in ERA patients is similar to other studies. Jousse-Joulin *et al*. studied US detected enthesitis in 26 consecutive JIA patients, of whom 9 were ERA patients and demonstrated enthesitis at 12.5% of the sites studied (2). Laurell *et al*. used US to detect enthesitis at the gluteal medius insertion at the posterior iliac crest in 27 children with ERA and found similar results (3). In a recently published cohort of 30 ERA patients, Weiss *et al*. showed that US proven enthesitis was present in 12.5% of patients with ERA (4).

Our observation of patellar tendon insertion and tendoachilles being the common entheseal site is similar to the previous two studies. Both studies showed that the common sites of enthesitis in these children were insertions of patellar tendon at tibial tuberosity, tendoachilles at calcaneum and quadriceps at superior pole of patella (2, 4). Humeral epicondyles has also been reported as a common site of invovlement however we did not include it in our study.

Lack of good concordance between clinical and ultrasound enthesitis has been noted both in studies in children as well as adults though ERA patients have been studied in only one previous study. In JIA physical examination had low sensitivity (50%) in the detection of US-proven enthesitis (2), even after the inclusion of a semi-quantitative measure such as dolorimetry in patients with ERA (4).

Two findings in our study need special mention. A higher prevalence of nearly 50% involved entheseal sites showing chronic changes as compared to none in a previous study is probably related to the longer median disease duration in our patients (4, 15). This is also re-

Table II. Ultrasound abnormalities detected at the various entheseal sites in ERA patients*.

Feature	No. (%) of sites with abnormality					
	Iliac crest	Quadriceps	Inferior pole of patella	Tibial tuberosity	Tendo-achilles	Plantar fascia
Thickening of tendon	0 (0)	4 (7)	2 (3)	5 (8)	7 (12)	7 (12)
Hypoechogenecity of tendon	0 (0)	5 (8)	1 (2)	7 (12)	6 (10)	4 (7)
Peritendinous edema	0 (0)	0 (0)	1 (2)	1 (2)	1 (2)	0 (0)
Bursitis	NA	0 (0)	NA	14 (23)	7 (12)	NA
Doppler signal	3 (5)	1 (2)	2 (3)	12 (20)	9 (15)	2 (3)
Tendon tear	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Loss of thickness	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Tendon calcification	0 (0)	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Bone erosion	0 (0)	4 (7)	1 (2)	7 (12)	9 (15)	2 (3)

*For each site, total of 60 entheses were examined in 30 ERA patients. More than one abnormality may be present at one site.

Table III. Agreement between clinical and ultrasound enthesitis.

Entheseal site*	Concordance (%)	Ultrasound enthesitis present, but clinical enthesitis absent (no. of sites)	Clinical enthesitis present, but ultrasound enthesitis absent (no. of sites)
Iliac crest	96.6	2	0
Superior pole of patella	88.3	7	0
Inferior pole of patella	95.0	2	1
Tibial tuberosity	83.3	9	1
Tendoachilles	85.0	5	4
Plantar fascia	88.3	4	3

flected in the higher median age at first visit suggesting that in developing countries the diagnosis or referral is often delayed.

The high discordance rates between physical examination and US were seen despite the presence of active inflammation in most (87%) of the lesions. This is of particular concern since enthesitis is an important diagnostic criterion for ERA. Appropriate classification has obvious important implications in treatment, screening for co-morbidities such as uveitis and prognosis. In our cohort, 7 patients had only ultrasound enthesitis. It would be of great interest to know whether detection of subclinical enthesitis is of relevance in diagnostic classification and whether these children who present with arthritis only, have disease course resembling ERA or oligoarticular/polyarticular JIA. With increasing use of anti-TNF agents and their proven high efficacy, accurate classification is of utmost importance for early institution of appropriate therapy (16). With US revealing considerable subclinical enthesitis, further consideration needs to be given as to whether it should be included in screening of patients with JIA.

Our study has certain limitations. The relatively small sample size, especially the healthy control cohort, is a limitation but it is at par with the largest study to date with ERA patients (4). Larger cohorts would need longer study periods. Another limitation was lack of confirmation of inter-rater and intra-rater observer variability in the US examination. This is due to limited trained manpower, heavy patient load and lack of time in our part of the world. Data from previous studies affirm the fact that US has high sensitivity and very good inter-rater and intra-rater reliability for the detection of enthesitis, both in adults and children (2, 4, 6, 7), when undertaken by trained personnel. The sonologist in our study was trained specifically in rheumatological ultrasound and hence this limitation is likely to be minor. The strength of the study lies in the inclusion of patients with one category of JIA.

In conclusion, enthesitis is common in ERA patients and US detects considerably more entheseal sites with involvement than physical examination. Future research should focus on the role of ultrasound in early diagnosis of JIA in general and ERA in particular.

Key messages

- Enthesitis is common in JIA-ERA patients, occurring in up to 83% of patients.
- Ultrasound detects considerably more entheseal sites with involvement than physical examination
- Role of ultrasound in early diagnosis of JIA-ERA needs to be explored.

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