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Ultrasound versus physical examination in predicting disease flare in children with juvenile idiopathic arthritis: a systematic literature review and qualitative synthesis

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Abstract

In this systematic review we analyzed the published articles related to the predictive value for flare of subclinical synovitis assessed by ultrasound (US) in juvenile idiopathic arthritis (JIA). Medline, Embase and Cochrane databases were searched from 1990 to 2020 by two authors, using PICO methodology. The study is built and reported according to PRISMA guidelines. Searches identified four articles comprising a total of 187 JIA patients in clinical remission from at least 3 months. Two of the articles found US subclinical signs of synovitis to be predictive for flare, with a five times higher risk (with Power Doppler signal as an important feature), while in the other two baseline US abnormalities did not predict a clinical flare. The articles differed for protocols, definitions, and length of follow-up. US has an expanding role in pediatric rheumatology, with interesting applications especially during the follow-up, potentially identifying subclinical inflammatory signs predictive of flare. However, the few studies available do not allow definite conclusions at this time.

Keywords: ultrasound; Juvenile Idiopathic Arthritis; flare; remission; subclinical synovitis

Introduction

Ultrasound (US) has gained widespread usage, since it is safe, cheap, easily available, non-invasive, free of ionizing radiations and able to allow a real-time scanning evaluation at bedside. In the last few years technological advances have improved the ability of US to visualize more superficial and deeper areas and to detect blood flow through small vessels, making it suitable for musculoskeletal applications and strongly increasing its use in rheumatology. US can closely image articular and periarticular structures and has become part of daily clinical practice for many rheumatologists. However, in growing subjects physiologic variants can create subtle pitfalls [1,2], and training with use of advanced equipment are necessary to limit potential misinterpretations [3].

Despite the expanding availability of this tool and beyond its technological limitations, a crucial question is its role in decision making, strictly linked to the expectations related to the use in routine care. The assessment of active arthritis and procedural guidance appear to be the main applications in the field, but if the support of US as a procedural guidance during arthrocentesis and corticosteroid injections is of proven utility, more controversial is its added value with respect to clinical examination in the detection of arthritis [4]. Even more intriguing for clini-

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cians is its potential contribution in treatment management [5]. Several studies have shown a high sensitivity of US for minimal signs of inflammation even in patients in apparent clinical remission [6-10], but the meaning of subclinical synovitis in terms of risk of flare, which would be crucial for the definition of treatment strategies is still to be defined [11]. In fact, in a study performed on rheumatoid arthritis (RA) patients who underwent a step-up disease-modifying antirheumatic drug escalation guided by US results, there was no significant improvement in outcome [12]. Other studies related to this topic have yielded conflicting results [13].

When considering juvenile idiopathic arthritis (JIA), a high percentage of paediatric patients show arthritis flare upon withdrawal of therapy and the availability of a tool able to guide decision-making related to stopping treatment strategies would be certainly needed [14]. However, in children the higher risk of US misinterpretations mostly linked to the anatomical peculiarities of a growing skeleton make the real significance of suspected findings still less clear than in adults. There have been few studies that have explored the ability of US to predict clinical flares in JIA. Our aim was to review published articles related to the predictive value of subclinical synovitis for arthritis flare in children affected by JIA in clinical remission.

Material and methods

The systematic review was conducted according to the recommendations of PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) as conveyed in Moher's guidelines [15]. The search question was if subclinical synovitis assessed by US is able to predict flare in children with JIA in clinical remission.

Medline, Embase and Cochrane databases were searched from 1990 to 2020. The search terms entered were: Juvenile Idiopathic Arthritis (JIA), Juvenile Rheumatoid Arthritis (JRA), Juvenile Chronic Arthritis (JCA), juvenile, child, children, adolescents, teenagers, youth, remission, clinical inactive disease as population, US as intervention, and subclinical synovitis, predictive value, flare, relapse as outcomes. All relevant index and natural language terms were tailored for all databases searched. In addition, further relevant references were manually searched if needed. The inclusion and exclusion criteria are summarized in table I.

After removal of duplicate results, the first screening process was done considering the title and abstract, and a further selection was done based on the full text. The review selection was independently performed by two reviewers (ODL and TG). The discrepancies were solved by discussion with a third reviewer (RC) involved in case of no consensus achieved. The information about the numbers of articles generated by using search terms, the numbers of articles ruled out after the first screening and the reason for any excluded article were inserted in a PRISMA flow chart.

Quality assessment

The articles that met all inclusion criteria were evaluated in relation to methodological quality. The Quality Assessment Tools used for the selected studies were the Consolidated Standards of Reporting Trials (CONSORT Statement; http://www.consort-statement.org/) [16] and the Quality in Prognosis Studies tool. 5-point Oxford Quality Rating Scale [17].

Results

The search found 208 records. After duplicate removals 168 records were reviewed on title and abstract and, of those, 162 were excluded. Six records were assessed for eligibility and 2 were excluded after full text reading 1 for wrong outcome and the other for insufficient data (fig 1). The final result consisted therefore of 4 articles, which are summarized in Table II.

The 4 articles [18-21] were published in the last 7 years and include a total of 202 patients (88 in the larger

Table I. Inclusion /exclusion criteria for screening titles and abstracts.

Inclusion criteria	Exclusion criteria
• Population: Diagnosis of juvenile idiopathic arthritis based on ILAR criteria; Age <16 years; Clinical remission of JIA	• Abstract only, Letters to Editor, Case reports (≤ 10 patients);
• Study design: Randomised controlled trials (RCTs); Systematic Reviews; Prospective studies; Case series (> 10 patients)	• When multiple articles were based on the same study population, we included only the most complete (or recent) one.
• Index test: Ultrasound plus clinical assessment of any joint	
• Reference: Clinical diagnosis of disease flare	
• Outcome: Clinical flare within 12 months	

Table II. Summary of the selected articles

Study	De Lucia O [18]	Miotto V [19]	Magni Manzoni S [20]	Zhao Y [21]
Publication date and study type	2018 Prospective, case control, multicentric	2017 Prospective, monocentric	2013 Prospective, case control, monocentric	2018 Prospective, monocentric
Clinically inactive patients: age (yrs) at baseline	10±4.3 clinically-inactive, US-positive 9.9± 4.4 SD Clinically-inactive, US negative	11.6±3.8	Median 11.9 (IQR 7.3-15.19)	Median 10.7 (8.9-12.5)
ILAR JIA categories (%)	46 (52) persistent oligoarticular 15 (17) extended oligoarticular 15 (17) RF neg polyarticular 12 (14) other	14 (40) persistent oligoarticular 12 (34.3) extended oligoarticular 9 (25.7) polyarticular	18 (46.1) persistent oligoarticular 12 (30.8) extended oligoarticular 4 (10.3) RF neg polyarticular 2 (5.1) ERA 2 (5.1) Psoriatic 1 (2.6) Systemic	10 (25) persistent oligoarticular 12 (30) extended oligoarticular J 15 (38) RF neg polyarticular 1 (3) RF positive polyarticular 2 (5) ERA
N clinically inactive patients (N patients off treatment) / N clinically inactive joints scanned at baseline	88 (28) / 3872 (44 joints per patient)	35 (9) / 3298 total assessed joints	24 (13) / 2028 total assessed joints	40 (5) / 289 total assessed joints
Duration of clinical inactive disease at baseline	0.9 years±0.6 in US-positives 1.9±0.8 years in US-negatives	1.9±2.2 years	minimum 3 months	1 year (0.5-1.8)
Observation period	4 years	30 months	2 years	Not reported (median 22 months)
N patients clinically inactive US positive at baseline	20/88 (22%) patients	24/35 (68.6%) patients	14/39 (35.9%) patients	18/40 (45%) patients
N joints clinically inactive US-positive at baseline	38 joints (0.98%)	122 joints (3.7%)	45 joints (2,2%)	24 joints (8.3%)
Clinically-inactive, US-positive patients/joints at baseline that flared (N, %)	15/20 (75%) patients	NA	15/39 (38.5%)	NA
Interval of relapse	NA	18/122 (14.7%) joints	17/45 (37.7%) joints	4/24 (16.6%) joints
Healthy controls	At 1 year 45% of US positive patients and 6% of US negative relapse	Mean 5.95 months (0.25-18)	Median 10.6 months (6.3-13.7)	Median 12 months (3-24)
Risk of flare in clinically inactive US positive patients	Enrolled	Not enrolled	Enrolled	Not enrolled
	Increased (with predictive value higher in presence of positive PD signal)	Increased only in presence of positive PD signal	Not increased	Not increased

N, number; PD, power Doppler; JIA, juvenile idiopathic arthritis; US, ultrasound; NA, not assigned; RF, rheumatoid factor; ERA, early rheumatoid arthritis

one). Age at baseline was homogenous (medians 10, 10, 11, and 11 years). In 3/4 studies the most prevalent ILAR category was persistent oligoarticular, while in the study by Zhao et al [21] RF-negative polyarticular JIA accounted for 38% of cases.

At the time of enrolment, number of patients off medications varied, being 57% in Magni Manzoni's analysis [20], 34% in De Lucia's, 25.7% in Miotto's [19] and 13% in Zhao's [21]. Methotrexate was the most used drug in patients under treatment.

Two of the studies [18,19] showed an increased risk of flare in patients who were US-positive at baseline, while the other two [20,21] could not show such predictive value. Interestingly, in the first two studies the risk of flare was similar, being about five times higher for patients who showed a positive baseline US when com-

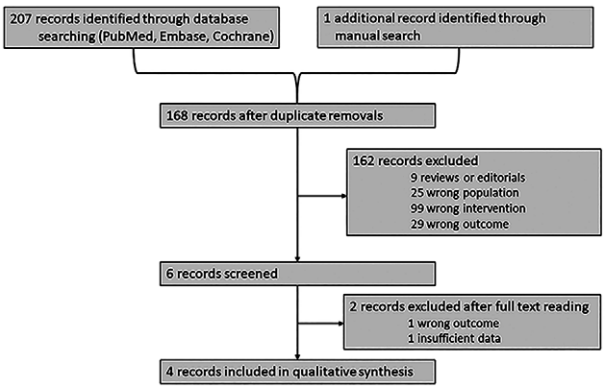

Fig 1. PRISMA flow chart

pared to the US-negative group. In the paper by De Lucia et al, however, the risk was higher at patient level but not at individual joint level. Of note, healthy controls were recruited only in two of the studies [18,20], one of which also included clinically active joints as positive controls [18].

Discussion

The use of US in paediatric rheumatology has gained wide attention, but its real role in clinical practice is still a matter of debate [22]. While its usefulness in detecting synovitis in difficult to examine joints such as the ankle and as guidance in arthrocentesis is now established [3,23], studies on other possible uses have yielded conflicting results [20,21]. It is claimed that it can detect subclinical synovitis [23-25], but without a gold standard such as histology or MRI the superiority of US when compared to clinical examination cannot be confirmed even if the experience maturated in RA of the adult [26] pushes us forward in this direction.

The possibility to predict disease flares with a non-invasive, radiation-free method such as US would be on the other hand very useful for the clinician, who in case of disease remission has few elements to judge when to taper medical treatment. Studies in this regard have been performed in RA [27,28], but data in JIA are scanty.

We performed a systematic review on this topic and could identify only 4 articles which met our inclusion criteria. Of these, 2 were in favour of an increased risk and two were not. Several factors could influence this discrepancy. Series included were not large, with a total of less than 200 patients altogether and 3 of the 4 articles including <40 cases. With regard to ILAR classification, the majority of cases were in the persistent oligoarticular JIA category, which is the most common, and the overall distribution reflects the epidemiology of the diseases also considering the ethnicity of the different series [29]. Studies were all prospective and in the only one which included more than one centre [18], the procedures were standardized. Of note, healthy controls are particularly important when scanning joints of a growing child and only two of the studies [18,20] included a control group. In one study not only negative but also positive controls were included [18]; this also would have been desirable since the presence of active synovitis can sometimes be difficult to distinguish from physiological vascularization in an immature joint [1,3]. Of note in the two works with a control group, the percentage of patients and joints with US detected subclinical synovitis at baseline were sensibly lower than the other (see table II).

The predictive value of PD signal in articular cartilage of JIA patients should be considered with caution due to the possibility of its misinterpretation, being this data also observed in healthy, growing children. Discordant results regarding this aspect also appear in the four articles analyzed in this metanalysis. In fact, De Lucia et al [18] observed an increased predictive value for relapse when grey scale findings were associated with PD abnormalities, Miotto et al [19] found the presence of PD signal essential for predicting the risk of flare, Zhao et al [21], documented abnormal PD signal only in a low percentage of children (without a correlation with disease flare), and Magni Manzoni et al [20], surprisingly found a greater frequency of PD signal in patients with persistent inactive disease with respect to those who flared.

Among the different factors which could influence the risk of relapse, duration of inactive disease and duration of follow-up varied among studies, which would also be possible bias in interpreting the results. Variations in medical treatment during the observation period was accounted for in the article by De Lucia et al [18], but not in the others. This is obviously another bias, since the risk of relapse can be influenced by the tapering or withdrawal of drug therapy.

While in RA studies have demonstrated that subclinical inflammation can be found on US in patients which are in clinical remission according to the clinical measures [30] and that US-detected residual synovitis can predict the risk of relapse and structural progression [31,32], in paediatrics this has not been definitely proven. Indeed, despite growing evidence supporting the potential role of US in the monitoring of patients, the use of US is still a matter of debate even in RA. Two recent RCTs (TASER and ARTIC) have demonstrated that a treatment strategy based on the US assessment did not lead to an improved clinical outcome in comparison with a conventional treat to target (T2T) approach, suggesting that the systematic use of US in the follow-up of RA patients would be not

justified [11,12]. In children many pitfalls linked to the structure, anatomy, and physiology of the growing joint make this type of study difficult to perform and interpret. The real question of whether US-detected subclinical synovitis is a risk factor for relapse, according to our study, cannot be answered both for the paucity of data and for discordance of results in the few articles included in the review.

First of all, studies which include a gold standard (if histology is not possible, at least MRI) would be necessary to judge the superiority of US when compared to clinical examination; second, a standardization of methodology is required d and is still not widespread; and third, appropriate positive and negative control groups are necessary in order to bypass as much as possible the interpretation biases that are so common in this regard.

Conflict of interest: none

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