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The role of Power Doppler ultrasonography in comparison with biological markers in the evaluation of disease activity in Juvenile Idiopathic Arthritis

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ABSTRACT

Objective: To evaluate the performance of Power Doppler Ultrasonography (PDUS) compared with biological markers, in the assessment of disease activity in children with Juvenile Idiopathic Arthritis (JIA). **Methods:** Forty hospital visits were studied comprising 32 patients with JIA, during one year of follow-up. Each patient underwent clinical, laboratory and ultrasound (PDUS) evaluation. The physician global assessment score on the visual analog scale (PhGA) was used as a standard for assessing disease activity, based on previous studies. The PDUS signal was scored according to a semiquantitative four grade scale (0-3). **Results:** PDUS assessment of synovial vascularisation was more sensitive than erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) in identification of the active disease: 90.4% vs. 57% and 28.5% respectively. CRP had a higher specificity (94%) in comparison with PDUS (89.5%). A significant association between clinical examination (PhGA) and PDUS score or ESR was found. Kappa statistics revealed a high level of agreement between PhGA and PDUS score (k=0.799) and a low level of agreement between PhGA and biological markers (k=0.356 and k=0.225 respectively). Patients with higher PDUS score (>/=2), ESR >/= 30mm/h or CRP >/= 2mg/dl were more likely to have active disease. **Conclusion:** Laboratory tests used today are not sufficiently sensitive for the prediction of active disease. PDUS assessment of synovial vascularisation is a technique with good sensitivity and specificity, thus it may be a beneficial criteria for evaluating disease activity in JIA, completing conventional clinical examination.

Keywords: juvenile arthritis, Power Doppler, disease activity, ESR, CRP

REZUMAT

Obiectiv: Obiectivul acestui studiu este de a evalua performanţele tehnicii Power Doppler în aprecierea activităţii bolii la copiii cu Artrită Idiopatică Juvenilă (AIJ), în comparaţie cu markerii biologici de inflamaţie. **Material şi metodă:** Au fost studiate 40 de vizite medicale, pentru 32 de pacienţi cu AIJ, urmăriţi pe o durată de un an. Fiecare pacient a fost evaluat clinic, biologic şi ecografic. Evaluarea globală a activităţii bolii (PhGA) a fost folosită drept metodă standard în aprecierea activităţii bolii. Semnalul Power Doppler a fost cuantificat semicantitativ cu ajutorul unei scale cu patru grade (0-3). **Rezultate:** Evaluarea vascularizaţiei sinovialei cu ajutorul PDUS este o metodă mai sensibilă decât viteza de sedimentare a hematiilor (VSH) şi proteina C reactivă (PCR) în identificarea bolii active: 90,4% versus 57% şi respectiv 28,5%. PCR a avut specificitate mai înaltă (94%), comparativ cu cea a PDUS (89,5%). S-a identificat o asociere semnificativă statistic între examinarea clinică (PhGA) şi scorul PDUS sau VSH şi o concordanţă foarte bună între examinarea clinică (PhGA) şi scorul PDUS (k=0.799). In schimb între PhGA şi markerii biologici concordanţa este redusă (k=0.356, respectiv k=0.225). Pacienţii cu scor PDUS mare (>/=2), VSH >/= 30mm/h sau PCR >/= 2mg/dl au o probabilitate mai mare de a avea boală activă. **Concluzii:** Testele de laborator utilizate azi nu sunt suficient de sensibile în identificarea bolii active. Determinarea gradului de vascularizaţie al sinovialei cu ajutorul PDUS este o metodă cu o bună sensibilitate şi specificitate. Astfel, poate fi un criteriu util în aprecierea activităţii bolii în JIA, completând examinarea clinică convenţională.

Cuvinte cheie: artrită juvenilă, Power Doppler, activitatea bolii, VSH, PCR

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Introduction

Juvenile idiopathic arthritis (JIA) is a broad term that describes a clinically heterogeneous group of arthritis of unknown cause, which begins before 16 years of age and persists for more than 6 weeks [1]. Studies in developed countries have reported a prevalence that varies between 16 and 150 per 100,000 [2].

Evaluation of disease activity is a fundamental component of the clinical assessment in children with JIA because persistently active disease plays a major role in causing joint damage and physical functional disability. Furthermore, measurement of the level of disease activity over time is important in assessing the effectiveness of anti-rheumatic drugs in clinical trials and in monitoring the patient's course in daily care [3].

Assessment of disease activity in JIA is primarily dependent on clinical evaluation and serum markers of inflammation, variables included in the core set established by the American College of Rheumatology (ACR) in 1997. This„core set of outcomes" is composed of the following 6 measures: physician global assessment of disease activity (PhGA), parent/patient global assessment of well-being, active joint count, restricted joint count, functional assessment and a laboratory measure of inflammation - the erythrocyte sedimentation rate (ESR) [4]. This is a useful instrument for evaluating improvement following a given treatment, but this core set does not provide a complete disease activity score and does not allow comparisons between patients [5].

There are authors which consider C-reactive protein (CRP) levels to be more sensitive for short-term changes in disease activity, whereas ESR can be influenced by a number of unrelated factors, such as age, gender or plasma proteins [6]. Therefore, there is a tendency to use CRP instead of ESR for estimating inflammation. Recently, studies on adults with rheumatoid arthritis validated the disease activity score (DAS) as a index for disease activity together with EULAR response criteria based on CRP, as an alternative to ESR [7].

At this time there is no„gold standard" to use in the diagnosis or for the measurement the disease activity in JIA. Studies of separate variables involved in the„core set of outcomes" have shown that the PhGA is the best variable for predicting disease activity [8] and is the most sensitive discriminator between high and low disease activity in JIA [9]. The PhGA seems to be the best indicator of disease flare [10] and also a variable with high interobserver agreement [11]. The PhGA is therefore suitable for a dependent variable and has also been used as one before [5].

Nowadays, US is increasingly used by the clinicians for the evaluation of joint disease. Power Doppler ultrasonography (PDUS) is a useful tool for imaging abnormal synovial vascular flow resulting from inflammation [12-15].

The purpose of this study was to investigate performance of PDUS assessment of synovial vascularisation in comparison with biological markers of inflammation (ESR and CRP), in the evaluation of disease activity in children with JIA. The standard for assessing disease activity was PhGA, rated on a 100 mm visual analog scale, based on previous studies [8-11].

Materials and methods

All 40 consecutive hospital visits of 32 patients who met the ILAR criteria for JIA [16], and who had attended the Department of Pediatrics in the 2nd Pediatric Clinic Cluj Napoca, Romania, between Octomber 2008- November 2009, were included in the study. Two patients were examined three times and four patients were examined twice through the duration of our study. Exclusion criteria were active extra-articular manifestations of JIA (systemic signs or uveitis) and other asociated autoimmune diseases. Informed consent was obtained from all patients or parents, as appropriate. The study was approved by the local Ethics Committee.

Clinical and laboratory assessment

The following data were recorded for each patient at each study visit: sex, age, ILAR category, disease duration, current treatment and active joints count. Clinical evaluation was performed by two pediatric specialists (NM, MS) prior to laboratory testing or ultrasound exam and reached consensus on PhGA score. The PhGA was rated on a 100 mm visual analog scale (VAS; where 0=no activity and 100=maximun activity). The active disease was considered when PhGA>0, and the inactive disease when PhGA=0. A joint with active disease was defined as the presence of swelling or tenderness/pain on motion and restricted motion [17].

Laboratory assessment included determination of ESR using Westergreen method with vacuum blood collection tubes and CRP level using the immunoturbidimetric method. Normal values for these laboratory methods were ESR<10mm/h and CRP 0-0,8mg/dl.

Ultrasonography

US assessment was performed in the same day with clinical and laboratory examination, by a clinician experienced in musculoskeletal US, blinded to the clinical and laboratory findings (DF). An Aloka Prosound alfa 10 ultrasound system and a 13 MHz linear transducer were used in this study. All joints with active arthritis on the clinical evaluation at the study visit or active at prior consultations were scanned for the presence of power Doppler signal. The area with the most pronounced power Doppler activity was identified. PDUS signal was scored according to a semiquantitative four grade scale 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), and 3=marked (pres-

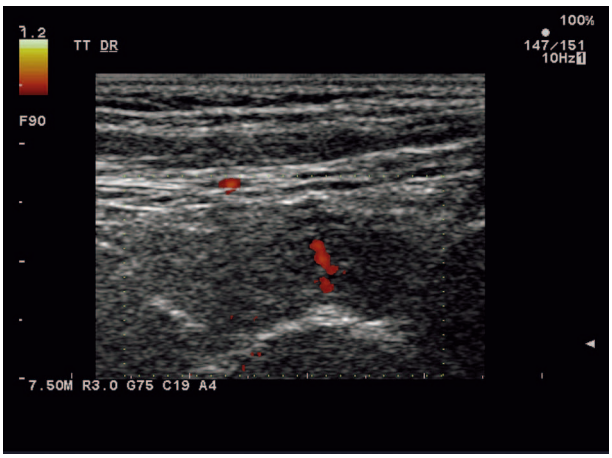

Fig 1. Mild vascularisation on power Doppler (score 1). Active proliferative synovitis of the right ankle in a 10 years girl with polyarticular JIA.

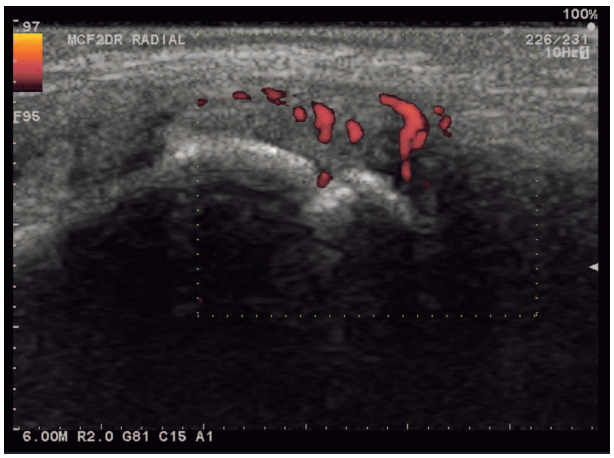

Fig 2. Moderate vascularization on power Doppler (score 2). Active proliferative synovitis of a metacarpophalangeal joint, in a 15 years girl with Rheumatoid Factor-positive polyarthritis.

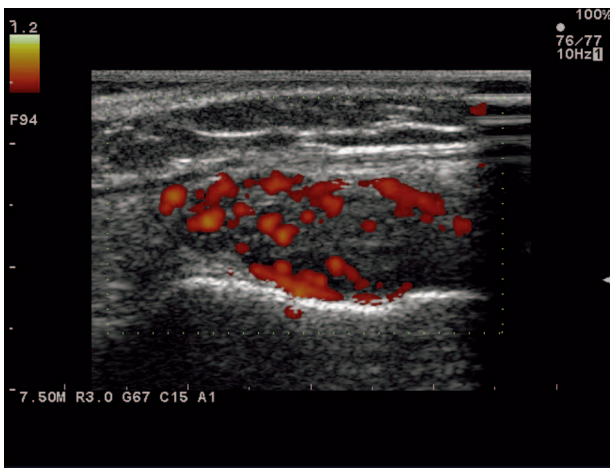

Fig 3. Marked vascularization on power Doppler (score 3). Active proliferative synovitis of the knee joint in a 15 years patient with persistent oligoarthritis.

ence of confluent vessel dots in more than half of the synovial area). Examples of the US grading system are shown in fig 1-3.

Statistical analysis

Numerical variables such as age and disease duration were summarized by mean and range. Dichotomous variables such as type of JIA or treatment were summarized as frequency (in percentage). The performance of PDUS, ESR and CRP in assessing active disease was made with determination of Sensibility, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and Youden index (Y). Results are expressed with 95% confidence intervals (95% CI). The association between PhGA and PDUS score/ESR/CRP was assessed using chi-square tests (Fisher's Exact Test and Pearson Chi-Square when <25% cells have expected count less than 5). To measure the strength of associations we used Cramer's V index and Contingency Coefficient, with their range between 0 and 1.0.

The agreement between PDUS, ESR and CRP was assessed using Kappa statistics. A kappa of 1 indicates perfect agreement, whereas a kappa of 0 indicates agreement equivalent to chance.

All statistical analyses were performed using SPSS 13.0

P values<0.05 were considered to be statistically significant.

Results

Clinical and laboratory findings

The mean age of the patients in our study was 11.6 years (range 1.8-20). Most children (20 of 32; 62.5%) had persistent oligoarthritis. The mean disease duration was 4 years (range 0.16-14.5). Eleven patients were without specific medication at the study visit, 4 of them were on steroids, 5 on Methotrexate and 4 patients were being treated with tumor necrosis factor inhibitors (table I).

According to PhGA, patients had active disease in 21 of 40 medical visits: 13 with mild (VAS 0-30 mm), 3 with moderate (VAS 30-60 mm) and 5 with severe JIA (VAS >30 mm).

ESR ranged from 4 to 56 mm/h (median 10mm/h). Only four visits were with an ESR over 30 mm/h. Among 21 hospital visits with active disease, 9 were with normal ESR. In inactive disease, ESR predicted 15 of 19 cases. The statistical measures of the performance of ESR in assessing active disease are presented in Table II. ESR between 11 and 29 mm/h predicted 66.6% and ESR>30 mm/h predicted 100% of active visits (Table III).

Table I. Demographic and clinical presentation of the patients in the study cohort*

Number of patients	32
Number of medical visits	40
Age (years)	
Mean (range)	11.6 (1.8-20)
Sex	
Female/Male	23/9
Type of JIA	
Persistent oligoarthritis	20 (62.5%)
Extended oligoarthritis	2 (6.25%)
RF-positive polyarthritis	4 (12.5%)
RF-negative polyarthritis	6 (18.75%)
Disease duration (years)	
Mean (range)	4 (0.16-14.5)
Treatment	
NSAID	8 pts (25%)
Steroids	4 pts (12.5%)
Methotrexat	5 pts (42%)
Tumor necrosis factor inhibitors	4 pts (12.5%)
Without specific medication	11 pts (34%)
PhGA	
Mean (range)	16.6 (0-80)
Disease activity	
Active (PhGA>0)	21 vts (52.5%)
Inactive (PhGA=0)	19 vts (47.5%)
Grading active disease according to PhGA	
Mild (VAS 0-30mm)	13 vts (32.5%)
Moderate (VAS 30-60mm)	3 vts (7.5%)
Sev	5 vts (12.5%)

* JIA = juvenile idiopathic arthritis, VAS =visual analog scale. NSAIDS = nonsteroidal antiinflammatory drug, RF = Rheumatoid factor, pt = patients, vt = medical visits, PhGA = Physician global assessment of disease activity

Table II. Statistical measures of the performance of ESR, CRP and PDUS in assessing active disease, in the study group*

Statistical parameters	ESR	CRP	PDUS
Sensibility (95% CI)	**0.57** (0.34- 0.78)	**0.285** (0.11-0.52)	**0.904** (0.70-0.98)
Specificity (95% CI)	**0.79** (0.54-0.93)	**0.94** (0.74-0.99)	**0.89**5 (0.67-0.98)
Positive Predictive Value (95% CI)	**0.75** (0.47-0.92)	**0.85** (0.42-0.99)	**0.90** (0.67-0.98)
Negative Predictive Value (95% CI)	**0.62** (0.40-0.81)	**0.54** (0.36-0.71)	**0.89** (0.67-0.98)
Youden index (95% CI)	**0.36** (0.08-0.64)	**0.23** (0.01-0.45)	**0.80** (0.61-0.98)

* ESR = the erythrocyte sedimentation rate, CRP = C-reactive protein, PDUS = Power Doppler ultrasonography, CI = confidence interval

Table III. The performance of different levels of ESR, CRP and PDUS in identifying active disease*

		Active Disease	Inactive Disease	Total	% Active
ESR (mm/h)	**</=10**	9	15	24	37.5%
	11-29	8	4	12	66.6%
	>30	4	0	4	100%
CRP (mg/dl)	**</=0.8**	15	18	33	45.45%
	0.9-2	2	1	3	66.66%
	>2	4	0	4	100%
PDUS	**0**	2	17	19	10.5%
	1	12	2	14	85.6%
	2	4	0	4	100%
	3	3	0	3	100%
	TOTAL	21	19	40	

* ESR = the erythrocyte sedimentation rate, CRP = C-reactive protein, PDUS = Power Doppler ultrasonography

Fisher's Exact Test demonstrated a significant association between PhGA and ESR (F=6.37, p=0.038<0.05, Pearson value 5.414, p=0.027<0.05). The same was revealed by values and the significance level of Cramer's index and Contingency Coefficient (Tabel IV). Kappa agreeement between PhGA and ESR was 0.356.

CRP ranged from 0.2 to 5.7 mg/dl (median 0.3 mg/dl). Only 4 visits were with a CRP of more than 2 mg/dl. From 21 medical visits with active disease, 15 were with normal CRP. CRP predicted 18 of 19 hospital visits with inactive disease. The statistical measures of the performance of CRP in assessing active disease are presented in Table II. CRP between 0.9 and 2 mg/dl predicted 66.6% (2 of 3) and CRP > 2 mg/dl predicted 100% of active visits (Table III).

Fisher's Exact Test demonstrated no association between PhGA and CRP (F=4.29, p=0.10>>0.05). The same was revealed by the values and significance level of Cramer's index and Contingency Coefficient. (Tabel IV) Kappa agreeement between PhGA and CRP was 0.225.

Ultrasonography

In 21 of 40 studied visits, vascularisation was detected. Synovial vascularisation was graded 1 in 14 visits, 2 in 4 visits and 3 in only 3 visits. From 21 visits with active disease, 19 had PDUS signal detected. Among 19 visits with inactive disease, 17 were correct predicted

Table IV. Associations between PhGA and ESR/CRP/PDUS for disease activity in 40 medical visits of patients with JIA*

	Chi-Square Tests **Fisher's Exact Test** **PhGA**	*Chi-Square Tests* **Pearson Chi-Square** **PhGA**	*Symmetric Measures* **Cramer's index** **Contingency Coefficient** **PhGA**
ESR	F = 6.37 p = 0.038<<0.05	X^2 = 5.414 p = 0.027<<0.05	Cramer's V = 0.411 Contingency Coefficient = 0.38
CRP	F = 4.29 p = 0.10 >>0.05	–	Cramer's V = 0.34 Contingency Coefficient = 0.32
PDUS	F = 26.169 p = 0.00<<0.05	–	Cramer's V = 0.805 Contingency Coefficient = 0.627

* PhGA=Physician global assessment of disease activity on visual analog scale, ESR=the erythrocyte sedimentation rate, CRP=C-reactive protein, PDUS=Power Doppler ultrasonography, JIA=Juvenile Idiopathic Arthritis

with Power Doppler. The statistical measures of the performance of PDUS in assessing active disease are presented in Table II. PD signal grade 1 predicted 85.6% but grade 2 and 3 predicted 100% of active visits (Table III).

Fisher's Exact Test demonstrated a significant association between PhGA and PDUS score (F=26.169, p 0.00<<0.05). The same was revealed by values and significance level of Cramer's index and Contingency Coefficient (Tabel IV). Kappa agreeement between PhGA and PDUS was 0.799. Kappa agreement was only fair when PD signal grade 1 was considered as inactive synovitis (K=0.322).

US synovitis in clinically asymptomatic joints was seen in two cases.

Discussions

Assessment of the disease activity in JIA and therefore therapeutic decisions are primarily influenced by the presence of synovitis on clinical examination, corroborated with laboratory tests of inflammation. But, in daily clinical practice these two findings often fail to be in accord, making the therapeutic decisions difficult.

As a complement to conventional clinical examination, US has been used to directly visualize and objectively quantify synovial inflammation. It has been suggested that it allows a marked improvement of the clinician's capability to detect both early and hidden features of synovitis [12]. More than Gray-scale sonography alone, power Poppler may be more representative of true synovitis, because the presence of power Doppler signal signifies increased synovial vascularity, associated with active joint inflammation [12-15,19].

Based on previous studies [8-11], we chose the PhGA as the standard for assessing disease activity, PhGA being determined by the presence or degree of the others variables in the „core set of outcomes" established by the ACR in 1997 [4].

Our findings emphasize the marked lack of agreement between clinical examination and laboratory tests. Among 21 visits with active disease, 9 were with normal ESR and 15 were with normal CRP. For inactive disease, prediction was best for CRP (18 of 19 hospital visits) and moderate for ESR (15 of 19). Disagreement may be partially due to the fact that, the study patients had, on average, a low level of disease activity. ESR was significantly associated with clinical examination, but with a low level of agreement between them in assessing active disease. Chi-square tests did not find any association between CRP and PhGA. These results support other studies [5] in revealing the laboratory tests used today, as not sufficiently sensitive. Notably, higher levels of ESR (>30mm/h) or CRP (>2mg/dl) are more likely to indicate active disease.

Comparing the usefulness of CRP and ESR levels as diagnostic parameters for active disease, ESR could better identify actual active disease, having a higher sensitivity than CRP. This finding is discordant with the general opinion that CRP levels are more sensitive to short-term changes in disease activity than ESR [6,7].

In contrast with biological markers, we found a significant association, with high level of kappa agreement between PhGA and PDUS score. Like ESR and CRP, higher PDUS score (> or =2) were more likely to demonstrate active disease. When we also considered PD signal grade 1 as inactive synovitis, level of agreement between PDUS and PhGA decreased, but still demonstrated significant association. PDUS was more sensitive than ESR and CRP in assessing active disease: 90.4% versus 57%

and 28.5% respectively. Therefore PDUS examination may have a greater benefit in standard clinical practice for monitoring JIA patients, than laboratory tests of inflammation.

Discrepancies between clinical examination and PDUS were found in four cases. Two cases had joint swelling on clinical evaluation and synovial hypertrophy on US examination but without PD activity. In the other two cases, we found mild PDUS signal in asymptomatic joints with chronic synovitis (subclinical synovitis). The number of joints with subclinical synovitis in our group would probably have been higher, if we had examined systematically a uniform number of joints for all patients, regardless of their medical history. The presence of subclinical synovitis has been demonstrated before in other adult or children studies [20-22].

The detection of subclinical disease has implications for deciding which patients are candidates to receive more aggressive therapy. Biologic agents are only licensed and recommended in children with active polyarticular JIA, unresponsive or intolerant to methotrexate [23]. Presence of subclinical synovitis may also lead to reclassification in some patients. According to the current ILAR classification of JIA, oligoarthritis and polyarthritis are defined on a basis of the number of affected joints (</=4 or >4, respectively) [16]. Moreover, this issue may affect the assessment of clinical remission. Recently developed preliminary criteria for inactive disease in JIA include no active arthritis, defined on clinical examination, normal ESR or CRP along with other criteria [24].

There are certain limitations of the present study. First of all, we could not use the MRI as the gold standard for identification of active disease in comparing the accuracy of clinical examination, biological markers and PDUS. Dynamic MRI is the most sensitive and specific diagnostic imaging technique for joint involvement. This is difficult to perform in children, because small children need sedation. Beside that, its limited availability, expense, and need for contrast administration makes its role in assessing and monitoring joint abnormalities in JIA necessary still to be under evaluation [25,26]. Another limitation is that we could not investigate the interobserver and intraobserver variability in PDUS evaluation. US examination is generally recognized as operator dependent. Finally, a larger group of patients would probably have strengthened the results.

Conclusions

We found that laboratory tests used today in standard clinical practice are not sufficiently sensitive in predicting active disease. PDUS assessment of synovial vascularisation is a technique with good sensitivity and specificity; thus it may be a beneficial criteria for evaluating disease activity in JIA, completing conventional clinical examination.

Competing interest
No conflict of interest.

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