THE ROLE OF MUSCULOSKELETAL ULTRASOUND IN MANAGEMENT OF JUVENILE IDIOPATHIC ARTHRITIS

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Abstract

Background: Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood and an important cause of acquired disability in children. In the recent years, musculoskeletal ultrasound (MSUS) has been regarded as a reliable method to precisely document and monitor the synovial inflammation process in patients with JIA.

Objectives: To evaluate the role of (MSUS) in detection and assessment of clinical and subclinical synovitis in patients with JIA.

Patients and Methods: This prospective cohort study was conducted in the Pediatrics and Physical medicine, Rheumatology and Rehabilitation Departments, Tanta University Hospital. The study included 20 children aged< 16 years diagnosed with JIA according to International League of Associations for Rheumatology (ILAR) criteria. Patients were assessed by MSUS and JADAS 10 at the initial diagnosis and reassessment 6 months after the start of treatment. All the studied patients were subjected to essential laboratory investigations initially and after 6 months of starting treatment.

Results: There was statistically significant value between MSUS findings and Patient grade according to JADAS 10 score. MSUS proved to have a significant role in detection of clinical and subclinical synovitis in JIA and a significant role for reassessment of patients to evaluate the efficacy of treatment. JIA proved to be more common in females. Arthritis and Arthralgia were the most common JIA manifestations in our study. Polyarticular RF- JIA was the most common type in our study.

Conclusion: MSUS has a great role in detection and assessment of clinical and subclinical synovitis in JIA, so it is used in early detection of JIA patients and used for assessment of disease activity in JIA patients after starting treatment.

Keywords: Juvenile idiopathic arthritis (JIA), musculoskeletal ultrasound (MSUS), Juvenile Arthritis Disease Activity Score (JADAS 10), subclinical synovitis.

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INTRODUCTION

Most cases of persistent rheumatic illness in children are caused by juvenile idiopathic arthritis (JIA). All kinds of arthritis that manifest before the age of 16 and persist for more than 6 weeks are classified as juvenile idiopathic arthritis (JIA). [(1)]

JIA encompasses a heterogeneous group of conditions, all presenting with damage to cartilage and bone from synovial inflammation that lasts too long and leads to significant functional impairment. [(2)]

Clinical and laboratory measures are relied upon for diagnosis of JIA and determining the prognosis for children with JIA. However, imaging techniques such as ultrasound showed a significant role in visualizing synovial inflammation, over the decade MSUS has been described by many rheumatologists as the stethoscope of the joint [(3)].

MSUS is widely recognized as a valuable tool for diagnosing and follow-up JIA patients, with special significance for the detection of subclinical synovitis, the capture of early articular damage , the enhancement of patient subclassification within JIA, and the guidance of intra-articular corticosteroid injections, . [(4)]

Owing to the importance and significant impairment of JIA, the aim of our study was to detect the role of ultrasonographic findings in detection of clinical and subclinical synovitis and its role in reassessment of patient response to treatment.

PATIENTS AND METHODS:

Twenty patients less than 16 years old with ILAR-diagnosed JIA were enrolled in this prospective cohort research at Tanta University Hospitals'

Pediatrics, Physical Medicine, Rheumatology, and Rehabilitation Clinics. The study was conducted between January 2022 and December 2022.

After receiving approval from Tanta University's Ethical Committee, the research was carried out. All participants in the research have their parents' written informed permission.

Exclusion criteria patients who had a different connective tissue disorder, such as juvenile dermatomyositis, juvenile lupus erythematosus, or a mixed connective tissue disorder, patients with neoplastic diseases and patients with septic arthritis.

Each participant had thorough history, Complete clinical examination, with special attention to musculoskeletal system, Laboratory investigations including complete blood count[5], Erythrocyte sedimentation rate (ESR) [6], C-reactive protein (CRP). [7], Serum ferritin. [7], Rheumatoid factor (RF). [8], Antinuclear antibodies (ANA), [9] and Anti cyclic citrullinated peptide antibodies (anti-CCP). [10] and Disease activity assessment By Juvenile Arthritis Disease Activity Score 10 (JADAS 10) [11] which includes the following four components:

1. Physician's global assessment of disease activity measured on a (0–10) visual analogue scale.
2. Patient/parent global assessment of well-being measured on a (0–10) visual analogue scale.
3. Active joint count
4. Erythrocyte sedimentation rate (normalized from 0–10). ESR readings below 20 mm/hour were set to 0 and those above 120 mm/hour were set to 10.

MSUS examination

All patients were examined at ultrasonography unit of Physical medicine, Rehabilitation & Rheumatology Department in Tanta University Educational Hospital using SAMSUNG MEDISON,Model: UGEO H60, Power: 100-240 V. 50/60 Hz, Made in: Korea with MFG date: 2013.01

In order to perform an ultrasound evaluation of most of the child's joints, we had him or her lie supine on the exam table. The youngest Children (< 5years old) may sit on their parents' lap in order to calm them but no sedation was required.

The joints were examined in the longitudinal and transverse planes using B-mode and Doppler ultrasound using linear multi-frequency transducer (dynamic range 9-13 MHZ) for assessment of synovitis (synovial hypertrophy, joint effusion and power Doppler (PD) signal). Certain anatomical features must have been captured in every suggested scan for it to be of any use.

LIMITATIONS:

MSUS evaluation has some challenges or limitations that should be in mind, these challenges made ultrasound not a validated tool for assessment of JIA activity in many studies. These challenges include:

- Operator dependency
- Equipment dependency
- The potential for artefacts misinterpretation
- Field of vision is restricted (cannot see the entire joint space).
- Challenging to execute when severe joint inflammation exists
- No pediatric-specific validated protocols
- Poor value in evaluating the TMJ and axial skeleton.

STATISTICAL ANALYSIS

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The Shapiro-Wilk test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). McNemar and Marginal Homogeneity Test used to analyze the significance between the different stages. Paired t-test used in normally distributed quantitative variables, to compare between two periods. Wilcoxon signed ranks test used in abnormally distributed quantitative variables, to compare between two periods**.** Significance of the obtained results was judged at the 5% level.

RESULTS:

The age of studied patients in this study is between 4 – 15 years with mean 7.7 ± 2.72 with Male: Female Ratio between1: 1.5 which shows that JIA mostly occurs in females. Regarding family history of Rheumatological diseases and positive consanguinity 25% of studied patients owned relatives with Rheumatological diseases.

As regard to the initial manifestation of our studied patients, arthralgia was present as the main JIA manifestation in 100% of studied patients, arthritis was in 65% of patients, systemic manifestation (hepatomegaly, splenomegaly, fever and/ or rash) were present in less percentage of the studied patients, and 10% of patients presented with uveitis as a complication of JIA. And according to the different types of JIA by EULAR criteria, 30% of our patients have Polyarticular RF- JIA, 20% have Polyarticular RF+ JIA , 20% have Systemic JIA, 20% have Oligoarticular persistent JIA, 5% have Oligoarticular extended JIA, and the remaining 5% of our patients have Enthesitis related arthritis.

Table (1): Comparison between the laboratory data of studied patients initially and after 6 months of treatment.

Laboratory data	Initially	After 6 m of treatment	Test of Sig.	p
Hb (g/dl)				
Min. – Max.	10.30 – 14.60	10.50 – 13.60	t= 1.190	0.249
Mean ± SD.	12.47 ± 1.22	12.11 ± 0.86		
PLT (×10^3/ ul)				
Min. – Max.	170.0 – 375.0	178.0 – 357.0	t= 0.585	0.565
Mean ± SD.	244.5 ± 58.56	254.0 ± 53.73		
TLC (×10^3/ ul)				
Min. – Max.	4.40 – 12.50	4.70 – 8.40	t= 2.942*	0.008*
Mean ± SD.	7.90 ± 2.05	6.41 ± 1.07		
ESR 1stH (mm/hr)				
Min. – Max.	7.0 – 60.0	3.0 – 40.0	Z= 3.928*	<0.001*
Median (IQR)	28.0 (16.0 – 42.50)	9.50 (5.50 – 23.0)		
ESR 2ndH (mm/hr)				
Min. – Max.	22.0 – 112.0	12.0 – 80.0	Z= 3.922*	<0.001*
Median (IQR)	53.0 (32.50 – 82.50)	20.50 (13.50 – 44.0)		
CRP (mg/ L)				
Min. – Max.	3.70 – 48.0	2.40 – 11.60	Z= 3.734*	<0.001*
Median (IQR)	11.15 (5.75 – 19.10)	4.40 (3.30 – 6.45)		
+ANA	2(10.0%)	2(10.0%)	McN	1.000
+Anti CCP	3(15.0%)	3(15.0%)	McN	1.000
+RF	5 (25.0%)	5 (25.0%)	McN	1.000
AST (u/l)				
Min. – Max.	16.0 – 36.0	16.0 – 78.0	Z= 0112	0.911
Median (IQR)	27.0 (20.50 – 30.50)	24.0 (20.50 – 29.50)		
ALT (u/l)				
Min. – Max.	10.0 – 25.0	9.0 – 34.0	Z= 0.468	0.640
Median (IQR)	17.0 (15.0 – 19.0)	15.50 (11.50 – 21.50)		
Ferritin (ng/ml) Min. – Max. Median (IQR)	29.90 – 237.0 89.40 (44.15 – 143.8)	24.80 – 158.0 46.05 (37.15 – 90.20)	Z= 3.621*	<0.001*

IQR: **Inter quartile range**; SD: **Standard deviation**; **t: Paired t-test;** Z: **Wilcoxon signed ranks test**; **McN: McNemar test;** p: p value for comparing between **initially and after 6 months;** *: Statistically significant at $p \leq 0.05$

There was significant difference between acute phase reactants (ESR, CRP and serum Ferritin) and TLC initially and after 6 months of treatment as there was significant decrease in their results 6 months after the start of treatment, with insignificant results concerning RF, ANA and Anti CCP.

Table (2): Treatment regimen of studied patients.

Treatment	Initially	After 6 m of treatment	Test of Sig.	p
NSAIDS	4(20.0%)	2(10.0%)	McN	0.500
Prednisolone	9(45.0%)	5(25.0%)	McN	0.125
Dose (mg/kg/day)				
Min. – Max.	1.0 – 2.0	0.60 – 1.50	Z= 2.023*	0.043*
Median (IQR)	2.0 (1.50 – 2.0)	1.20 (1.0 – 1.40)		
Methotrexate	15(75.0%)	14(70.0%)	McN	1.000
Dose (mg/kg/week)				
Min. – Max.	10.0 – 15.0	10.0 – 15.0	Z=0.341	0.733
Median (IQR)	15.0 (14.0 – 15.0)	15.0 (12.0 – 15.0)		
Etanerecept (0.8mg/kg/week)	0(0.0%)	3(15.0%)	McN	0.250
Adalimumab (24mg/m^2/week)	1(5.0%)	4(20.0%)	McN	0.250
Topical steroid eye drops	0(0.0%)	2(10.0%)	McN	0.500

IQR: **Inter quartile range**; **McN: McNemar test**; Z: **Wilcoxon signed ranks test;** p: **p value for comparing between Start and end**

Methotrexate is the most common used DMARD in treatment of JIA patients and there was difference in the dose of Methotrexate initially and after 6 months of starting treatment. Regarding Biological DMARDS, results showed that Adalimumab and Etanerecept were the most common used Biological DMARDS nowadays. Corticosteroids Prednisolone was the most commonly used steroid and there was significant difference between its doses initially and after 6 m of starting treatment also many patient stopped steroid and turned to other drugs. Topical Corticosteroid Eye Drops were used in patient with uveitis.

Table (3): JADAS 10 of studied patients initially and after 6 m of treatment

JADAS 10	initially	After 6 m of treatment	T	P
Min. – Max.	12 – 36	9 – 26	10.203*	<0.001*
Mean ± SD.	24.95 ± 8.1	18.05 ± 5.79		
Inactive	0(0%)	2(10%)	24.50*	0.002*
Mild	7(35%)	10(50%)		
Moderate	7(35%)	8(40%)		
High	6(30%)	0(0%)		

SD: **Standard deviation**; **t: Paired t-test;** p: p value for comparing between **Start** and **End** *: Statistically significant at $p \leq 0.05$

There was significant difference in JADAS 10 score initially and after 6 months of starting treatment, as there was decrease in JADAS 10 score and patient grade according to JADAS 10 score after 6 m of starting treatment.

Table (4): Number of inflamed joints by musculoskeletal examination and EULAR-OMERACT combined scoring system of MSUS initially and after 6 months of treatment.

Number of joints		Initially	After 6 months of treatment	Z	p
by musculoskeletal examination	Arthralgia				
	Min. – Max.	1.0 – 7.0	0.0 – 5.0	3.824*	<0.001*
	Median (IQR)	4.0 (2.0 – 5.0)	2.0(0.0 – 2.50)		
	Arthritis				
	Min. – Max.	0.0 – 4.0	0.0 – 3.0	3.314*	0.001*
	Median (IQR)	2.0(0.0 – 2.50)	0.50(0.0 – 1.0)		
EULAR-OMERACT combined scoring system of MSUS	Grade 1				
	Min. – Max.	0.0 – 7.0	1.0 – 7.0	2.546*	0.011*
	Median (IQR)	5.0 (3.0 – 6.0)	4.0 (2.0 – 5.0)		
	Grade 2				
	Min. – Max.	0.0 – 5.0	0.0 – 5.0	2.840	0.005*
	Median (IQR)	2.0 (1.50 – 4.0)	2.0 (1.0 – 3.0)		
	Grade 3				
	Min. – Max.	0.0 – 4.0	0.0 – 4.0	1.841	0.066
	Median (IQR)	0.50 (0.0 – 2.0)	0.0 (0.0 – 1.0)		

IQR: **Inter quartile range**; Z: **Wilcoxon signed ranks test;** p: p value for comparing between **initially and after 6 months;** *: Statistically significant at $p \leq 0.05$

There was significant improvement in musculoskeletal manifestation after 6 months of treatment. There was also significant difference in number of inflamed joints in EULAR-OMERACT combined scoring system of MSUS especially in grade (1, 2) synovitis initially and after 6 months of starting treatment. Also there was difference between the numbers of inflamed joints that detected by MSUS and clinically, using MSUS EULAR-OMERACT combined scoring system helped to find more inflamed joints than the number of joints detected clinically.

DISCUSSION:

Chronic inflammation inside the joints is a hallmark of JIA, and it can develop to destroy cartilage, bone, and soft tissues, potentially resulting in severe impairment. [4] Improvements in JIA management have resulted from substantial therapy advancements during the past two decades. [12]

Evaluation of the disease status on clinical and analytical assessments of children with JIA. Many pediatric rheumatic disorders have made great strides in our understanding of their causes and treatments in recent years. [13]

Imaging techniques such as ultrasound showed a significant role in visualizing synovial inflammation, synovial hypertrophy, joint swelling, cartilage wear, bone degradation, and tenosynovitis. [14,15]

Patients' age in this research ranged from 4 to 15 years old. (60%) of them were females and eight (40%) of them were males, with Male: Female Ratio (1.0: 1.5)**.** This agreed with **Klein et al,** [16] who found that 80% of autoimmune diseases affect females.

Regarding classifications of JIA, 30% of our patients were Polyarticular RF-, 20% were Polyarticular RF+, 20% were Oligoarticular persistent, 5% were oligoarticular extended, 20% were systemic and 5% were ERA. This was in agreement with **Abdwani et al,** [17] who discovered that polyarticular JIA RF negativity was the most common subtype among JIA patients in Oman (39.2%), followed by oligoarticular JIA (31.8%), systemic JIA (17.8%), polyarticular JIA RF positivity (7.5%), ERA (3%) and psoriatic arthritis (0.9%), in contrast **Abou El-Soud et al,** [18] reported that oligoarticular JIA was the most common subset of JIA (52.2 %), followed by polyarticular JIA (29.5 %), and systemic JIA (13.6 %), and then finally, ERA (4.5 %) of the total JIA patients.

Patients with JIA in our research exhibited significant decrease in TLC, as well as ESR, CRP and serum Ferritin in JIA patients after 6 months of treatment. **Tugal et al,** [19] reported useful laboratory investigations in JIA include CBC and 1inflammatory markers like ESR and CRP which increased during the inflammation. Positivity for rheumatoid factor (RF) was found in of 25% of studied patients, Anti CCP was positive in 15% of patients and ANA was positive only in 10% of them. **Lipińska et al,** [20] discovered that children with longer durations of illness (56% vs. 40%) were more likely to test positive for anti-CCP antibodies. Moreover, anti-CCP antibodies were detected more frequently than traditional rheumatoid factor more than three or almost four times.

Regarding Juvenile Disease Activity Score (JADAS 10): 35% of studied JIA patients were of mild activity, 35% of them were of moderate activity and 30 % of them were of high grade activity initially, after 6 months of starting treatment these results turned into 10% of the studied patients were inactive, 50% of patients were mild grade, 40 % of patients were moderate grade and none of the studied JIA patients were categorized as high grade. These results show a significant response of JIA patients to treatment.

In our study, compared to a physical exam, MSUS has been demonstrated to be more reliable in detecting clinical and subclinical synovitis in children with JIA. Improving the initial categorization and subsequently the therapeutic management of JIA is possible by a multi-joint MSUS test performed at the time of diagnosis. **Wakefield, R. J. et al,** [21] MSUS detected more synovitis than clinical examination in patients with oligoarthritis. In almost two thirds of patients there was evidence of subclinical disease while one third could be reclassified as polyarticular.

Borocco et al, [22] Improving the initial categorization and subsequently the therapeutic management of JIA is possible by a multi-joint MSUS test performed at the time of diagnosis.

Synovitis was graded in our study division into None (Grade 0), Mild (1), Moderate (2), and Severe (3) and this was done according to grey scale mode, power Doppler mode and EULAR-OMERACT combined scoring system for grading synovitis in rheumatoid arthritis, and this was approved by **Lanni, Stefano, et al,** [23] in his study of the role of ultrasound in JIA.

MSUS showed a significant role in evaluation of synovitis in JIA patients , and it has its advantages over other imaging modalities for usage in pediatric patients, such as non-invasiveness, quick performance, ease of repetition, high patient acceptance, and absence of exposure to ionizing radiation. In addition, screening younger children does not need sedation. Therefore, MSUS is a more sensitive approach for diagnosing synovitis, tenosynovitis, and erosive bone disease than clinical examination and conventional radiography.

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