Research Article

Early Detection and Outcome Prediction of Juvenile Idiopathic Arthritis

Faten M. Ismail*, Ayman F. Darwish*, Ashraf M. Osman, Abdou S. Ellabban*, Fatma A. Mohamed*, Ahmed Hamed* and Moustafa Abdel Kader***.**

* Department of Rheumatology and Rehabilitation, Minia University.
** Department of Clinical pathology, Minia University.
*** Department of Radiodiagnosis, Minia University.
Contact: Ahmad Hamed, Rheumatology and Rehabilitation department, Minia University hospital, Tel. ٠١٠٠٩١٧٤٠٣٩, E.mail: ahmedrheumatology٢٠٠٠@yahoo.com.

Abstract

Introduction: Juvenile Idiopathic Arthritis (JIA) is a heterogenous group of arthritides affecting children under the age of ١٦ years. It is important to find ways to diagnose patients early in order to use active treatment modalities before damage has occurred**.** Also identifying predictors of poor outcome in JIA children may help to target therapies to those most likely to have poor outcomes. **Objective,** to determine whether early clinical, laboratory and musculoskeletal ultrasound (MSUS) characteristics can be used as early detectors and outcome predictors of JIA. **Methods,** this study comprised ٤٠ patients with JIA diagnosed according to the ILAR criteria, and ٢٠ healthy control individuals. All patients were subjected to the following assessments at base line and at follow up after ٦ months; clinical, laboratory and radiological evaluation, MSUS examination, assessment of disease activity and outcome measures. **Results,** musculoskeletal ultrasonography is highly sensitive for early detection of joint involvement in JIA and screening with US can identify subclinical disease. Number of joints with US synovitis was significantly correlated with different clinical features, disease activity and outcome measures. Children with JIA have reduced cartilage thickness, compared with healthy children. **Conclusion,** many clinical, laboratory and musculoskeletal ultrasonographic findings can be used as early detectors and outcome predictors of JIA patients.

Key words: Juvenile idiopathic arthritis, early detection, outcome prediction.

Introduction

Juvenile idiopathic arthritis is a chronic inflammatory disease that affects ١ of every ١,٠٠٠ children worldwide[١]**.** Joint inflammation has a central role in the development of cartilage damage and bony erosion in JIA[٢]. The presence of subclinical disease in some joints may alter patient classification or affect the identify-cation of patients requiring more aggressive treatment[٣]**.** Musculoskeletal Ultrasonography (MSUS) is increasingly used by clinicians for the evaluation of joint disease. It has been shown to be sensitive in the detection of synovitis and bone erosion in both small and large joints[٤,٥]**.** Outcomes of children with chronic arthritis have progressively improved over the past ٤٠ years[٦,٧]. Identifying predictors of poor outcome in JIA children may help to target therapies to those most likely to have poor outcomes and avoid over treatment in those most likely to have good outcome[٨].

Patients and methods

Forty patients with JIA and twenty subjects as a control group were included in this study; the patients were (٢٥) females and (١٥) males. All patients were diagnosed according to the ILAR criteria[٩]. ***All patients were subjected to:*** Initial assessment at base line and follow up assessment after ٦ months, where the

Following assessments were done for all patients at base line and at follow up:
(١) Clinical evaluation (full history and examination),
(٢) Radiological evaluation: Simple Erosion Narrowing Score (SENS) was used for X-ray scoring[١٠],
(٣) Musculoskeletal Ultrasonographic examination: Was done for all patients at the ١st presentation and at follow up and for the control; the following data were recorded for the right and left metacarpophalangeal joints, proximal interphalangeal joints, wrists, knees and ankles (effusion, bone erosion, synovial membrane thickness, articular cartilage thickness and power Doppler signal),
(٤) Laboratory evaluation: The following laboratory investigations were done for patients (at base line and at follow up) and control [CBC, ESR, RF, ANA titer and pattern (by immunofluorescent technique)[١١] and Anti Cyclic Citrullinated Peptide (Anti-CCP) antibody[١٢],
(٥) Disease activity and outcome measures as follow:
Assessment of disease activity was done for all JIA patients at base line and at follow up using the JADAS-٢٧[١٣]. The JADAS cut-off corresponding to inactive disease (remission) was ١ for all children, otherwise the disease is considered to be active[١٤]. Functional assessment of patients according to the CHAQ Disability Index (CHAQ-DI).

In our study, a CHAQ-DI >٠.٥ was selected to indicate poor functional outcome (moderate to severe levels of disability). Assessment of patient quality of life using the JAQQ score. In our study, higher JAQQ scores (٣-٧) were selected to indicate worse quality of life. Physician global assessment of disease activity measured on anchored horizontal ١٠ cm scale. Parent/patient general evaluation of wellbeing measured on anchored horizontal ١٠ cm scale. Assessment of pain using the parent or, when appropriate, the patient visual analogue scale measured on anchored horizontal ١٠ cm scale.

Statistical analysis

Data were coded, entered and analyzed by the Statistical Package for the Social Sciences (SPSS for windows version ١٦.٠)[١٥]. Two-tailed tests were used throughout, and statistical significance was set at the conventional level of less than ٠.٠٥. Regression analysis was used to determine outcome predictors.

Results

Among the ٤٠ JIA patients, ٦ patients (١٥٪) had systemic onset subtype, ٨(٢٠٪) oligoarticular extended, ٩(٢٢.٥٪) oligoarticular persistent, ٥(١٢.٥٪) polyarticular RF +ve, ٦(١٥٪) polyarticular RF –ve, ٥(١٢.٥٪) enthesitis related subtype and only one patient (٢.٥٪) had psoriatic JIA (PsJIA).

At base line ٤٤(١٣.٧٪) of the clinically normal joints had evidence of subclinical synovitis, i.e., had synovitis on US, and ٤٥(١٧.١٧٪) of the clinically normal joints had evidence of subclinical synovitis at follow up. We found that MSUS led to classify ٤ patients (had only arthralgia on clinical examination) as oligoarticular subtype, and also US led to classify ٢ patients (had no clinical synovitis) as polyarticular RF +ve, and another ٢ patients as polyarticular RF -ve JIA. The overall sensitivity and specificity of clinical examination for detecting synovitis were ٣٤.٥٪ and ١٠٠٪ respectively, while sensitivity and specificity of the MSUS for detecting synovitis were ٤٥.٧٪ and ١٠٠٪ respectively. Both at base line and at follow up the number of joints with US synovitis had positive highly significant correlation with many clinical (table ١). At base line and at follow up the number of joints with US synovitis had positive highly significant correlation with disease activity and outcome measures (table ٢). The mean cartilage thickness measured in the JIA patients at follow up was significantly lower in all examined joints compared with the healthy control group (figure ١), and there was significant decrease in the mean cartilage thickness of the patients measured at follow up as compared to measures at base line (figure ٢).

In regression analysis; the most significant independent predictor of active disease at ٦ months (JADAS-٢٧>١) was the base line VAS, followed by Par GE then duration of MS. The most significant independent predictor of poor CHAQ-DI at ٦ months (CHAQ-DI>٠.٥) was the Par GE, followed by VAS, Phys GA, ESR, JAQQ score, CHAQ-DI at base line, number of joints with US synovitis, then CRP, while the most significant independent predictor of poor JAQQ score at ٦ months (٦ months JAQQ≥٣) was the ESR, followed by JAQQ score at base line, duration of MS, then CRP. In general our study revealed that the systemic onset, polyarticular RF +ve and ERJIA subtypes had the worst outcome regarding disease activity, functional and quality of life outcomes, followed by oligoarticular extended and polyarticular RF –ve subtypes, while the oligoarticular persistent and PsJIA subtypes had the best results regarding disease activity, functional and quality of life outcomes. Predictors of extension (in oligoarticular JIA) included; the number of swollen joints, number of tender joints, ESR, JADAS, CHAQ-DI, JAQQ score, Par GE, and VAS (at base line). ANA positivity and the number of joints with US synovitis were the most significant predictors of persistent oligoarticular JIA. Anti-CCP positivity was the most significant independent predictor of polyarticular RF +ve subtype. Number of joints with clinical synovitis was the most significant independent predictor of polyarticular RF -ve subtype. Skin rash, fever and thrombocytosis were the most significant predictors of systemic onset subtype, while the most significant predictor of ERJIA (at ٦ months) was positive family history.

Table ١: Correlation between the number of joints with US synovitis and different clinical parameters (at base line and at follow up):

Clinical features	Number of joints with USS			
	At base line		At follow up	
	r	p	r	p
N. of swollen joints	٠.٩٦	٠.٠٠٠**	٠.٩١	٠.٠٠٠**
N. of tender joints	٠.٥١	٠.٠٠٠**	٠.٦١	٠.٠٠٠**
N. of joints with clinical synovitis	٠.٩٦	٠.٠٠٠**	٠.٠١	٠.٠٠٠**
N. of joints with Limited range of motion	٠.٤٤	٠.٠٠٤**	٠.٤٢	٠.٠٠٦**
Ritchie articular index	٠.٩٧	٠.٠٠٠**	٠.٩٨	٠.٠٠٠**
Duration of morning stiffness	٠.٤٠	٠.٠٠٠**	٠.٥٨	٠.٠٠٢**

** Significant P-value <٠.٠١
USS= ultrasonic synovitis. r= Pearson correlation.

Table ٢: Correlation between the number of joints with US synovitis and disease activity & outcome measures (at base line and at follow up):

Clinical features	Number of joints with USS			
	At base line		At follow up	
	r	p	r	p
JADAS-٢٧	٠.٣٥	٠.٠٠٣**	٠.٥٦	٠.٠٠٠**
CHAQ-DI	٠.٤٧	٠.٠٠٢**	٠.٦١	٠.٠٠٠**
JAQQ score	٠.٤١	٠.٠٠٢**	٠.٥١	٠.٠٠١**
Phys GA	٠.٤٢	٠.٠٠٦**	٠.٥٤	٠.٠٠٠**
Par GE	٠.٤٧	٠.٠٠٢**	٠.٥٤	٠.٠٠٠**
VAS	٠.٤٥	٠.٠٠٣**	٠.٥٧	٠.٠٠٠**

** Significant P-value <٠.٠١
USS= ultrasonic synovitis. r= Pearson correlation
JADAS-٢٧= juvenile arthritis disease activity score-٢٧
CHAQ-DI=childhood health assessment questionnaire
JAQQ score=Juvenile arthritis quality of life questionnaire

Phys GA=physicisn global assessment of disease activity
Par GE=parent general evaluation of wellbeing
VAS=visual analogue scale

Figures

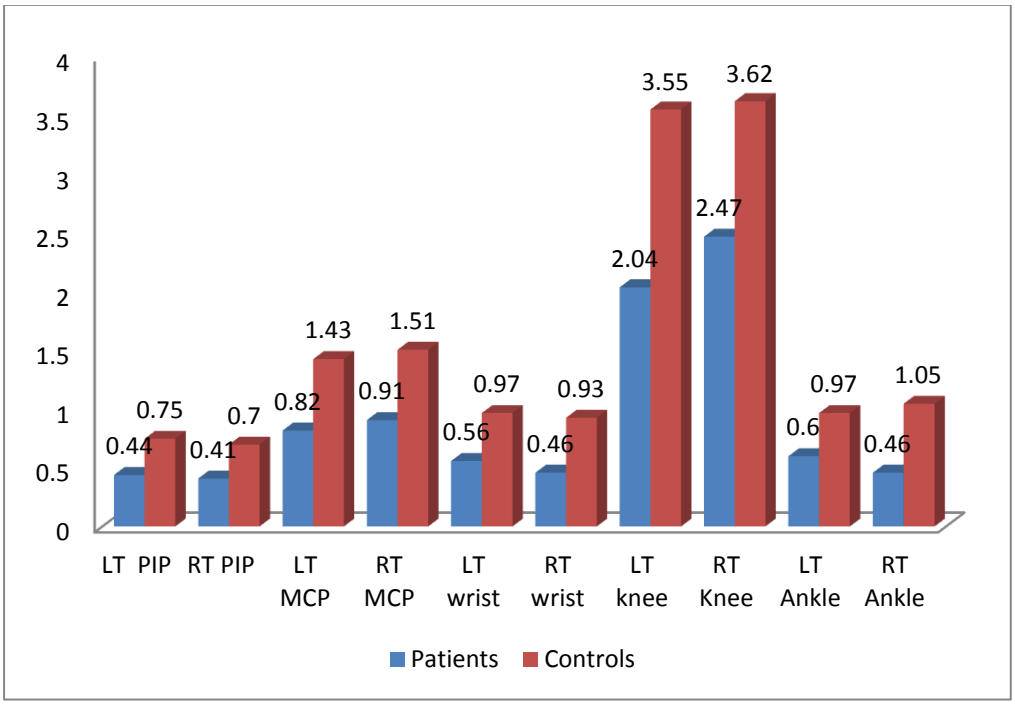

Figure ١: Comparison between joint cartilage thickness measured by MSUS in patients (at follow up) and control group (Values are in mm):

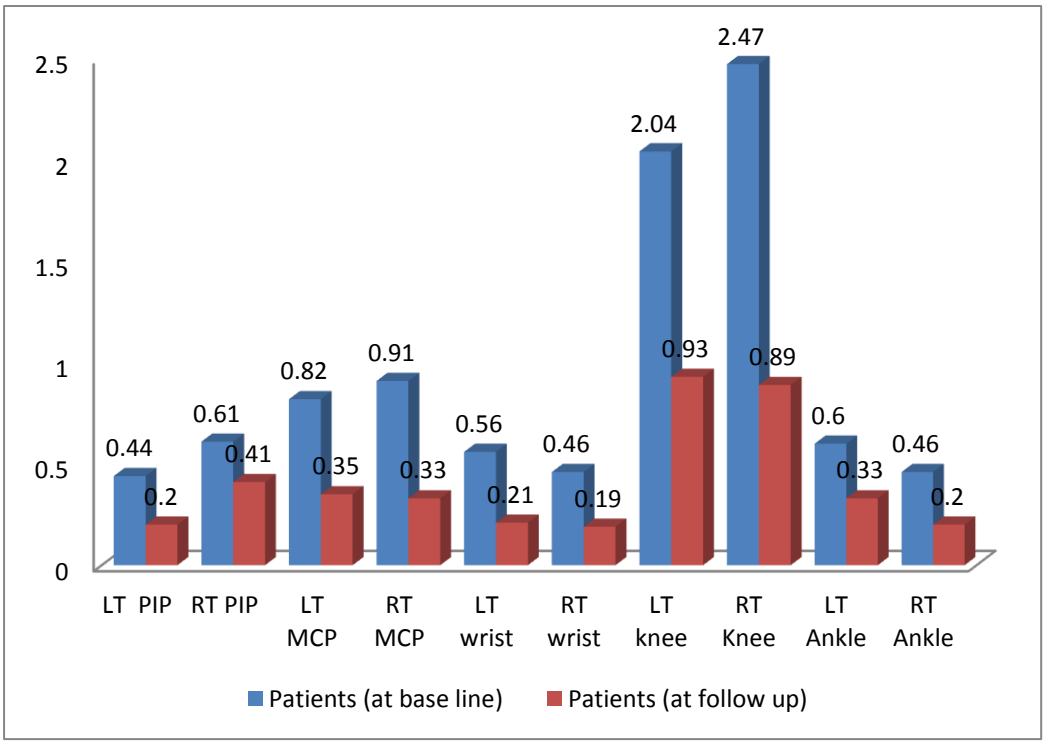

Figure ٢: Comparison between joint cartilage thickness measured by MSUS in patients at base line and at follow up (Values are in mm):

Discussion

Our data support previous studies which indicate that US is able to detect subclinical disease[١٦,١٧,١٨]. Silvia et al.,[١٩] compared clinical and US examination of multiple joints in children with JIA. They found that US detected more synovitis than clinical examination. ٨٦ (٥١.٥٪) of the ١٦٧ joints that had US documented synovitis were clinically normal (i.e., had subclinical synovitis). Our results goes in concordance with the study by Ginger et al.,[٢٠] who concluded that physical examination is neither highly sensitive nor specific for identifying active synovitis when compared to US, and screening with US can identify subclinical disease. Similar to our results, in the study of Silvia M et al.,[١٩] US led them to classify ٥ patients who were labeled as having oligoarthritis or were found to have no synovitis on clinical examination as having polyarthritis. In another study in JIA, ٣٦٪ of clinically normal knees had evidence of effusion on US[٢١].

In agreement with our results, Oen et al.,[٢٢] found that baseline JAQQ score was an independent predictor not only of the ٦ month JAQQ score, but also of disease status and physical function, they also found that disease duration and pain were also important predictors, correlating with physical function and quality of life outcomes. In concordance with our results, Kimme et al.,[٨] found that the strongest predictor of disability at ١ year was the level of disability at the first presentation, which likely encompasses many other features of the disease, including active joint counts and pain. In contrary to our findings Flato et al.,[٢٣] found an association between higher levels of disability among girls at ١ year. While Minden et al.,, [٢٤] In support of our findings, failed to observe any relationship between sex or age at onset and disease activity or disability in JIA patients. In agreement with our results, Adib et al.,[٦] concluded that persistent oligoarticular course have a better prognosis in terms of higher remission rates and better functional outcome than other subtypes. Ruperto et al.,[٢٥] found that systemic onset and polyarticular RF +ve subtypes had significantly greater impaired function as compared to other subtypes. While, In contrary to our results, in only one study polyarticular onset was found to have significantly better function than oligoarticular and systemic subtypes[٢٣]. Ravelli and Martini,[٢٦] found that, specific correlates for systemic JIA were persistent systemic features and thrombocytosis at ٦ months following presentation. Al-Matar et al.,[٢٧] found that predictors of extension included; symmetric disease, elevated ESR and disease duration. Flatø et al.,[١٦] found that male predominance and increased occurrence of sacroiliitis and enthesitis in ERJIA were significantly different from the same characteristics of patients with oligoarthritis and polyarthritis**.**

Conclusion

MSUS is highly sensitive for early detection of joint involvement in JIA when compared to physical examination, and screening with US can identify subclinical disease which may have important implications for patient classification. Number of joints with US synovitis was significantly correlated with different clinical features, disease activity and outcome measures. Children with JIA have reduced cartilage thickness, measured with MSUS, compared with healthy children. Clinical measures of disease and patient or parent completed measures early in disease course can be used to predict important ٦-month outcomes in children with JIA. The systemic onset, polyarticular RF +ve and ERJIA subtypes had the worst outcome regarding disease activity, functional and quality of life outcomes. Many measures can predict extension in oligoarticular JIA.

Recommendations

We recommend the use of MSUS for early detection of synovitis in JIA. Further studies on larger numbers of patients and longer periods of follow up are needed to determine if both early disease measures and short term outcomes are predictive of

long term outcomes. Follow up of the studied cohort will determine if the outcomes seen in this study are maintained or improved in the long term. The use of JADAS-٢٧, CHAQ, JAQQ, Phys GA, Par GE and VAS in early assessment and follow up of JIA patients is recommended.

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