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PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

Pakistan Journal of Biological Sciences 13 (3): 101-113, 2010
ISSN 1028-8880

Serum S100A12 and Temporomandibular Joint Magnetic Resonance Imaging in Juvenile Idiopathic Arthritis Egyptian Patients: A Case Control Study

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Abstract: This study aimed to measure serum levels of the proinflammatory protein S100A12, investigate clinical as well as contrast enhanced magnetic resonance imaging findings of temporomandibular joint inflammation among juvenile idiopathic arthritis patients and to find out the correlation between each of them, moreover with different disease parameters as temporomandibular joint inflammation may occur without clinical manifestations; it is in need for thorough evaluation and S100A12 may be a future anti-inflammatory treatment in JIA. Twenty patients with Juvenile Idiopathic Arthritis (JIA) and 10 healthy control subjects underwent measurement of S100A12 serum concentrations by sandwich ELISA. Temporomandibular Joints (TMJs); clinical and post contrast Magnetic Resonance Imaging (MRI) examinations were performed. MRI findings were scored. Results showed that TMJ arthritis was detected in 80% of JIA patients using MRI. Serum S100A12 levels were significantly increased in patients compared to controls. Serum concentrations of S100A12 and total MRI scores were significantly higher in JIA patients with active disease compared to those without activity. Systemic and polyarticular JIA patients showed significant increase in S100A12 levels and total MRI scores compared to those with oligoarticular JIA. The MRI TMJ abnormalities revealed significant association with clinical signs of TMJ inflammation but not with symptoms. A significant correlation was found between serum S100A12 concentrations and MRI score as well as between each of them and different clinical, laboratory disease parameters. Serum S100A12 levels showed significant positive correlation with synovial enhancement score. To conclude TMJ arthritis could be detected in most cases of JIA patients using contrast enhanced MRI. Increased S100A12 levels may point to synovial inflammation. Clinical signs of TMJ arthritis may be used as filter for MRI examination. Further studies on larger scale of JIA patients are needed for monitoring TMJ inflammation and S100A12 may be a potential target of future anti-inflammatory therapy.

Key words: Juvenile idiopathic arthritis, S100A12, contrast enhanced magnetic resonance imaging, temporomandibular joint, synovial inflammation

INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) is arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks (Petty *et al*., 2004). It is a chronic and heterogenous disease characterized by prolonged synovial inflammation that may lead to alterations in joint structures. Permanent changes may also develop in extraarticular organs and systems such as the eye (as a complication of chronic anterior uveitis) or the kidney (due to systemic amyloidosis), or may result from side effects of medications (Viola *et al*., 2005).

JIA encompasses several disease categories with diverse signs, symptoms and genetic complexity (Wallace *et al*., 2004). The International League of Associations for Rheumatology (ILAR) has revised the classification of JIA in Edmonton 2001. It included the following categories : systemic arthritis, oligoarthritis persistent or extended, polyarthritis rheumatoid factor positive, polyarthritis rheumatoid factor negative, psoriatic arthritis, enthesitis related arthritis and undifferentiated arthritis (Petty *et al*., 2004). All joints can be involved in JIA including the temporomandibular joint (TMJ). Involvement of the TMJ was first reported in 1897 by Still when he described chronic arthritis in childhood.

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The reported frequency of TMJ affection varied in literature depending on the population investigated, the subtypes of JIA represented and the method by which TMJ disease is diagnosed. In all subtypes of JIA, one or both TMJs can be affected and may even be the initial joint involved (Martini *et al*., 2001).

S100A12 (Calgranulin C) is a member of the S100 protein family which are acidic proteins of low molecular mass characterized by cell type specific production and the prescence of calcium binding domains (Foell *et al*., 2007). Human S100A12 is predominantly expressed and secreted by neutrophil granulocytes. Intracellular S100A12 upon calcium dependent activation interacts with target proteins to regulate cellular functions. Extracellular S100A12 shows cytokine like characteristics. It is markedly over expressed in inflammatory compartments and elevated serum levels of S100A12 were found in patients suffering from various inflammatory, neurodegenerative and neoplastic disorders. It's interaction with the multiligand receptor of advanced glycation (RAGE) and it's soluble form (sRAGE) plays a central pathogenic role. Several clinical evidences suggest a high potential of S100A12 as a sensitive and specific diagnostic marker of inflammation. An increase in it's concentrations have been found in serum of patients with rheumatoid arthritis (Pietzch and Hoppmann, 2009). Imaging remains an important tool in the assessment of juvenile arthritis patients. With improved treatment options, imaging must be very sensitive in detecting both inflammatory and destructive changes. Magnetic Resonance Imaging (MRI) in particular can detect synovitis and adds significant information to the clinical examination particularly in TMJ and foot joints (Graham, 2005).

The objective of this study is to measure serum levels of the proinflammatory protein S100A12 secreted by human neutrophils, moreover to find out clinical as well as contrast enhanced MRI findings of TMJ arthritis among JIA patients aiming to know the correlation between each of them and also to different disease parameters as TMJ inflammation may occur without manifestations; it is in need for thorough evaluation and S100A12 may be a future anti-inflammatory treatment in JIA.

MATERIALS AND METHODS

The present study included twenty patients (12 girls and 8 boys) with Juvenile Idiopathic Arthritis (JIA). Their age at the start of the study ranged from 7.5-17.0 years. Patients had either oligoarticular, polyarticular or systemic-onset JIA according to the criteria of the International League of Associations for Rheumatology (ILAR) (Petty *et al*., 2004). They were attending the Pediatric immunology, Rheumatology and Rehabilitation outpatient clinics in Ain Shams University Hospitals. Ten age and sex matched apparently healthy subjects were enrolled in the study as a control group. This study had started on 8th of January, 2008 and finalized on 12th of December, 2009.

Patients with cardiac pacemakers, metal implants or dental braces were excluded from the study.

After informed consent was obtained from patients or their legal guardians and the study was approved by Ain Shams Medical Ethics Committee (FMASU REC). All patients were subjected to the following:

Full history taking

Clinical examination: Thorough general and musculoskeletal examination were done for all patients with special emphasis to skin rash, fever, ocular affection, hepatosplenomegaly, number and distribution of affected joints.

A clinical activity score was assigned (Tselepis *et al*., 1999) based on the presence of joint swelling, warmth, redness, range of motion, pain, morning stiffness and the use of anti-inflammatory medications. The score ranged from 0 to 5 with 0 representing no complaints or physical findings of active disease and no use of anti-inflammatory medications and 5 representing very active clinical disease and the use of anti-inflammatory medication. The disease was defined as active if the score was ≥ 3 and inactive if the score was ≤ 2.

Functional ability was assessed using Childhood Health Assessment Questionnaire (C-HAQ): which describes the child's usual activities in 8 domains over the past week. It includes dressing and grooming, arising, eating, walking, with or without aids or assistive devices, hygiene, reach, grip and activities. Each question is scored from 0 to 3, (0 = no difficulty. 1 = some difficulty. 2 = much difficulty, 3 = unable to do). The score for each of the 8 functional areas were averaged to calculate the Disability Index. Patients were classified as mildly disabled (score < 1), moderately disabled (score 1 to 2) or severely disabled (score > 2) (Singh *et al*., 1994).

Pain assessment using a visual analogue scale (Mantha *et al*., 1993).

Clinical assessment of TMJ: Patients were asked about history of TMJ pain at rest or on movement (e.g., opening or chewing), morning stiffness longer than 15 min and crepitations. Clinical examination included : detection of joint tenderness (by palpation on the area infront of ear trigs and external acoustic meatus (Billiau *et al*., 2007)), crepitations (by using a stethoscope while the patient is asked to perform movement of the TMJ) (Billiau *et al*.,

2007). The maximal jaw mobility was assessed by maximal interincisal mouth opening (MIO): upon maximal mouth opening, a millimeter ruler was used to measure the vertical distance from the incisal edge of the upper maxillary incisor to the opposing mandibular incisor adding the vertical overbite. The MIO was considered to be restricted when ≤40 mm (Agerberg, 1974).

Laboratory investigations: Complete hemogram analysis and differential blood count using coulter JS plus cell counter (Coulter Electronics, FL, USA).

Erythrocyte Sedimentation Rate (ESR) using Westergreen method.

C-Reactive Protein (CRP) quantitative determination (Gmbh,Hannover,Germany).

Rheumatoid Factor (RF) detection (Plasmatec lab. products limited).

Antinuclear antibodies (ANA) by Immunofluorescence assay (Immuno- Diagnostics -USA).

Determination of serum S100A12 concentrations by sandwich enzyme linked immunosorbent assay (ELISA) (Maxisorp; Nunc. Hamburg, Germany) according to manufacturer instructions.

Samples collection: Eight milliliter of venous blood were withdrawn from each patient and subjects of the control group. Two milliliter were added onto EDTA tube for differential blood count and ESR. The remaining 6 mL were allowed to clot for serum separation.

Imaging study of TMJ by MRI: The MRI was carried out using a 1.5 Tesla Signa Horizon magnet. The examination was performed with a TMJ coil. The MRI evaluation included coronal T_1 and T_2 weighted images, sagittal T_1 and T_2 weighted images and after injection of gadolinium-based contrast medium, sagittal and coronal fat saturated T_1 weighted images. The variables evaluated were enhancement of the synovial membrane, condylar morphology, presence of pannus and intraarticular fluid. Enhancement of the synovial membrane which indicates synovial hyperplasia was defined as an increase in signal intensity of the synovium comparing the precontrast image with the post-contrast image. Pannus was defined as an intermediate signal of intraarticular mass on the precontrast T_1 weighted images. Intraarticular fluid (effusion) was defined as low signal intensity mass within the joint cavity. The MR variables were scored as follows for each joint: enhancement (0 = no enhancement, 1 = slight enhancement, 2 = strong enhancement), condylar morphology (0 = no erosions, 1 = mild erosions, 2 = severe erosions), pannus (0 = no visible pannus, 1 = small amount of pannus, 2 = large amount of pannus) and intraarticular fluid (0 = no fluid, 1 = small amount of fluid, 2 = large amount of fluid). The maximum total MR score could therefore be 8 per joint or 16 per patient (Küseler *et al*., 2005). The control group were subjected to MRI of TMJs without contrast.

Statistical analysis: This was done using SPSS 10 for Windows (Statistical Package for the Social Sciences). Descriptive statistics: mean, standard deviation, minimum, maximum and range of numerical data. Frequency and percentage of non-numerical data. Independent sample Student's t test was used to test the difference between two groups (for continuous variables). Chi square test to compare between groups regarding non numerical variables. Correlation (Pearson correlation coefficient r) assessing strength and direction of the linear relationship between two variables. One way Analysis of Variance (ANOVA) test (F) was used to test difference between more than two means. $p<0.05$ is considered significant and $p<0.001$ indicates high significance.

RESULTS AND DISCUSSION

This study was conducted on 20 patients with JIA. 10 apparently healthy subjects with matched age and sex have constituted the control group.

Among patients of this study; 12 were girls (60%) and 8 were boys (40%). Similarly the control group was composed of 6 females (60%) and 4 males (40%).

The mean age of patients in this study was 14.32±2.27 years with a range 7.5-17.0 years. While the control group was 14.50±2.87 years and a range of 9.0-17.0 years. Whereas the mean age of patients at disease onset was 9.27±2.84 years, ranging between 3.5-14.0 years. Disease duration of JIA patients showed a mean of 5.05±2.41 years and a range from 1.0 to 11.0 years.

This study included 3 patients (15%) with systemic onset JIA (quotidian fever, rash, arthritis, hepatosplenomegaly and lymphadenopathy). Three patients (15%) with oligoarticular onset JIA and 14 patients (70%) with polyarticular onset JIA. One female with polyarticular onset JIA showed uveitis, hypertension and amyloidosis.

The mean disease activity score of JIA patients was 3.35±1.08, while Child Health Assessment Questionnaire (C-HAQ) showed a mean of 0.96±0.48. The mean value of visual analogue scale for pain was 1.43±0.59. Whereas the mean number of active joints was 4.25± 1.71.

Antinuclear antibodies (ANA) were detected in 5 JIA patients. Within the polyarticular group; 5 patients were positive for rheumatoid factor and 9 patients showed negative results regarding rheumatoid factor.

The mean level of serum S100A12 among JIA patients was 666.0±391.37 ng mL^{-1} while in the control group it was 81.5±27.99 ng mL^{-1}.

Table 1: The frequency of clinical symptoms and signs of temporomandibular joint in juvenile idiopathic arthritis patients

Symptoms	No.	%	Signs	No.	%
Pain at rest	3	15	Tenderness	5	25
Crepitations	2	10	Crepitations	4	20
Pain on jaw movement	4	20	Decreased MIO	5	25
Morning stiffness	4	20			

No.: Number, %: Percentage, MIO: Maximal interincisal opening. Tenderness on palpation and decreased maximal interincisal opening were the most frequent clinical signs of temporomandibular joint affection

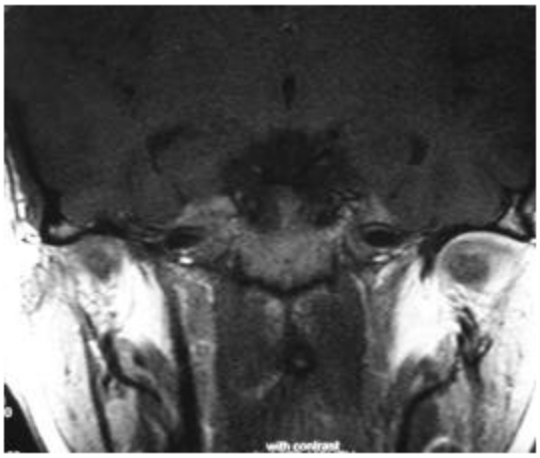

Fig. 1: Magnetic resonance imaging T_1 weighted image with contrast. It shows synovial enhancement of both temporomandibular joints more on left side in a patient with juvenile idiopathic arthritis

Temporomandibular joint clinical parameters showed that symptoms were present among 8 JIA patients (40%): 3 patients (15%), 2 patients (10%) complained of TMJ pain at rest and crepitations respectively. While pain on jaw movement and morning stiffness >15 min were symptoms in 4 patients (20%) for each of them (Table 1). Moreover, clinical examination revealed signs of TMJ involvement in 12 patients (60%) manifested by tenderness on joint palpation in 5 patients (25%), crepitations on movement in 4 patients (20%) and decreased maximal interincisal opening (MIO) in 5 patients (25%) (Table 1). The mean value of MIO among JIA patients was 43.0±4.93 mm while that of controls was 53.33±1.11 mm. No clinical symptoms or signs of TMJ disease could be detected in the control group.

Contrast enhanced MRI was done for 20 patients (40 TMJs): 16 patients (80%) showed MRI abnormalities while 4 patients had no MRI findings. The mean total score for MRI among JIA patients was 5.05±4.21.

Synovial enhancement (Fig. 1) showed the highest frequency among findings of contrast enhanced MRI, it was detected in 16 patients (80%), 31 TMJs (77.5%) with a mean score 2.60±1.60 While joint effusion (Fig. 2) was present in 13 patients (65%), 19 TMJs (47.5%) with a mean score 1.40±1.46. Whereas pannus and erosions were found in 5 patients (25%) for each but in 9 joints (22.5%), 7 joints (17.5%), respectively with a mean score of pannus 0.60±1.18 and erosions 0.45±0.94 (Table 2). Among JIA patients; there were 4 patients without clinical signs on TMJ examination but MRI abnormalities were detected in them. Regarding the control group, no TMJ abnormalities were found by MRI examination.

Table 2: The frequency of magnetic resonance imaging findings in juvenile idiopathic arthritis patients and temporomandibular joints

	Patients		TMJs	
Signs	No.	%	No.	%
Synovial enhancement	16	80	31	77.5
Joint effusion	13	65	19	47.5
Pannus	5	25	9	22.5
Erosions	5	25	7	17.5

TMJs: Temporomandibular joints. No.: Number, %: Percentage. Synovial enhancement showed the highest frequency among contrast enhanced magnetic resonance imaging findings

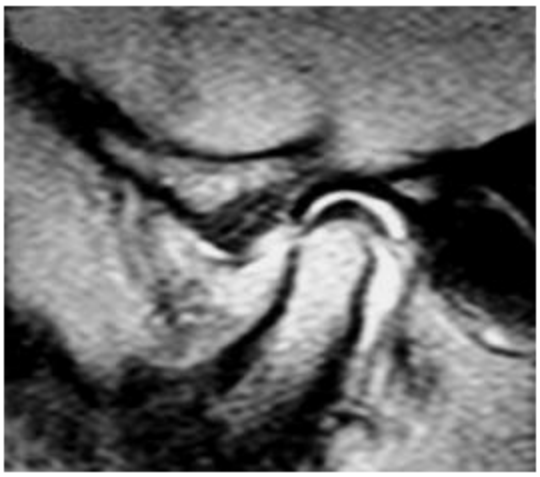

Fig. 2: Magnetic resonance imaging T_2 weighted image. It shows effusion of temporomandibular joint in a patient with juvenile idiopathic arthritis

Comparative studies

Comparison between patients and controls: No significant difference was found between both groups regarding age. The mean value of MIO was highly significantly decreased in patients than controls. While the mean serum levels of S100A12 showed high significant increase among JIA patients compared to controls ($p<0.001$) (Table 3).

Comparison between patients regarding disease activity: There was a significant increase in the mean of C-HAQ, pain score, serum S100A12 concentrations, effusion score and total MRI score in patients with active disease in

Table 3: Comparison between patient and control groups regarding demographic, clinical and laboratory parameters

Variables	Controls Mean±SD	Patients Mean±SD	t-value	p-value	Sig.
Age (years)	14.50±2.87	14.32±2.27	0.18	>0.05	NS
MIO (mm)	53.33±1.11	43.0±4.93	6.1	<0.001	HS
Neut. Count ($\times 10^9$ mL^{-1})	4.91±0.65	5.24±0.52	1.5	>0.05	NS
Hb (g dL^{-1})	13.05±1.33	10.62±0.90	5.8	<0.001	HS
ESR (mm h^{-1})	7.5±2.59	61.30±37.11	4.5	<0.001	HS
Serum S100A12 (ng mL^{-1})	81.5±27.99	666.0±391.3	4.6	<0.001	HS

MIO: Maximal interincisal opening, Neut: Neutrophil, Hb: Haemoglobin, ESR: Erythrocyte sedimentation rate. There were high significant differences between both groups regarding maximal interincisal opening and serum S100A12 levels. NS: Not significant, HS: Highly significant

Table 4: Comparison between juvenile idiopathic arthritis patients with active disease and without activity regarding demographic, clinical, laboratory and magnetic resonance imaging data

Variables	Active disease No. = 14 Mean±SD	Inactive disease No. = 6 Mean±SD	t-value	p-value	Sig.
Age (years)	14.35±2.64	14.25±1.25	0.09	>0.05	NS
Age at disease onset (years)	9.67±2.43	8.33±3.72	0.96	>0.05	NS
Disease duration (years)	4.67±2.21	5.91±2.83	1.05	>0.05	NS
No. of active joints	4.50±1.45	3.66±2.25	0.99	>0.05	NS
C-HAQ	1.17±0.40	0.46±0.19	4.04	<0.05	S
Pain score	1.68±0.52	0.85±0.22	3.7	<0.05	S
MIO (mm)	40.78±3.57	48.16±3.65	4.2	<0.05	S
ESR (mm h^{-1})	80.64±25.8	16.16±3.06	6.0	<0.001	HS
CRP (mg mL^{-1})	28.35±6.55	6.66±0.81	7.9	<0.001	HS
Serum S100A12 (ng mL^{-1})	836.78±334.99	267.50±134.41	3.9	<0.05	S
Syn. enhancement score	3.42±0.93	0.66±1.03	5.8	<0.001	HS
Effusion score	2.0±1.35	0.0±.00	3.5	<0.05	S
Pannus score	0.85±1.35	0.0±.00	1.5	>0.05	NS
Erosions score	0.64±1.08	0.0±.00	1.4	>0.05	NS
Total MRI score	6.92±3.58	0.66±1.03	4.1	<0.05	S

No: Number, C-HAQ: Child health assessment questiounaire, MIO: Maximal interincisal opening, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, S: Significance, Syn.: Synovial, MRI: Magnetic resonance imaging. A significant increase in serum S100A12 concentrations and total magnetic resonance imaging score for active juvenile idiopathic arthritis patients compared to the inactive group. NS: Not significant, S: Significant, HS: Highly significant

comparison to those who were not in the active stage of disease. The MIO was significantly decreased in patients with active disease. While a high significant increase in ESR, CRP levels and enhancement score could be detected among JIA patients with activity compared to those with inactive disease. No significant difference was detected between both groups regarding neutrophil count or haemoglobin level (p>0.05) (Table 4).

Comparison between different subgroups of JIA: Using analysis of variance test; there was significant increase in the mean of disease activity score, pain score, ESR, CRP levels, serum S100A12 concentrations (Fig. 3) in patients with systemic onset followed by polyarticular onset then

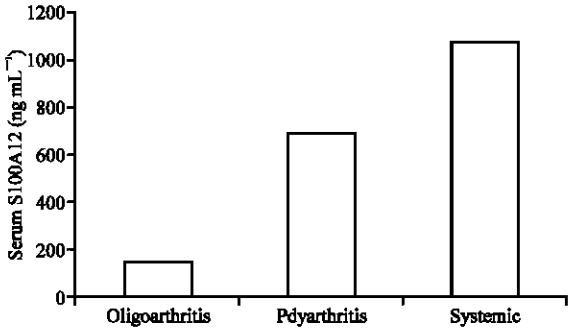

Fig. 3: Comparison between 3 subtypes of juvenile idiopathic arthritis. There is significant increase in serum levels of S100A12 in systemic and polyarticular types compared to oligoarticular type

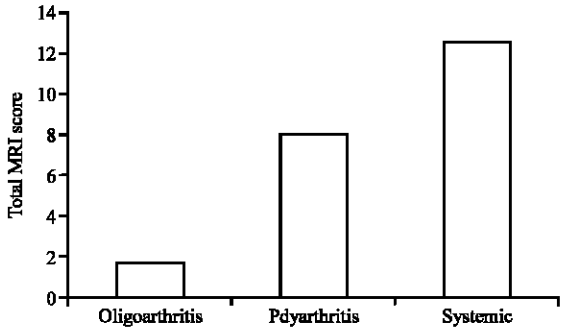

Fig. 4: Comparison between 3 subtypes of juvenile idiopathic arthritis. There is high significant increase in total magnetic resonance imaging score in systemic and polyarticular types compared to oligoarticular type

oligoarticular JIA. While the mean MIO was significantly decreased among systemic JIA group in comparison to other subtypes. Moreover, total MRI score showed the highest significant increase among systemic JIA patients then polyarticular type while the lowest score was detected within oligoarticular group (Fig. 4). No significant difference could be found between the 3 subtypes regarding neutrophil count or haemoglobin level (p>0.05) (Table 5).

Comparison between polyarticular RF+ve and RF-ve JIA patients: No significant differences could be detected between both groups regarding age (t = 1.4, p>0.05), disease duration (t = 1.2, p>0.05), disease activity score (t = 0.07, p>0.05), MIO (t = 0.09, p>0.05), serum S100A12 levels (t = 0.62, p>0.05) and total MRI score (t = 0.81, p>0.05). Polyarticular RF+ve patients were significantly

Table 5: Comparison between systemic, polyarticular, oligoarticular juvenile idiopathic arthritis subtypes regarding demographic, clinical, laboratory and magnetic resonance imaging findings

Variables	Systemic JIA Mean±SD	Polyarticular JIA Mean±SD	Oligoart. JIA Mean±SD	F-value	p-value	Sig.
Age (years)	12.16±4.07	14.78±1.83	14.33±1.52	1.7	>0.05	NS
Age at dis.ons (years)	8.00±4.09	10.03±2.25	7.00±3.60	1.9	>0.05	NS
Dis. duration (years)	4.16±0.76	4.75±2.43	7.33±2.51	1.7	>0.05	NS
No. of active jts	2.00±1.0	5.28±0.46	1.66±0.57	77.2	<0.001	HS
Dis. activity score	4.33±0.57	3.42±1.01	2.00±0.00	5.09	<0.05	S
C-HAQ	1.33±0.28	0.99±0.47	0.46±0.30	2.9	>0.05	NS
Pain score	1.83±0.73	1.50±0.51	0.70±0.17	3.9	<0.05	S
MIO (mm)	37.33±0.57	42.85±4.14	49.33±3.21	7.5	<0.05	S
ESR (mm h^{-1})	106.30±35.92	61.50±29.2	15.33±4.16	7.6	<0.05	S
CRP (mg mL^{-1})	35.00±2.0	22.28±10.06	6.66±0.57	7.7	<0.05	S
S.S100A12 (ng mL^{-1})	1070.00±480.3	691.07±295.61	145.00±8.66	6.9	<0.05	S
Syn. enhan. score	4.00±0.0	2.57±1.65	1.33±1.15	2.3	>0.05	NS
Effusion score	3.33±0.57	1.28±1.32	0.00±0.0	6.2	<0.05	S
Pannus score	2.66±1.52	0.28±0.72	0.00±0.0	11.2	<0.05	S
Erosion score	2.33±1.15	0.14±0.36	0.00±0.0	24.3	<0.001	HS
Total MRI score	12.33±2.08	4.28±2.99	1.33±1.15	13.8	<0.001	HS

Oligoart: Oligoarticular, JIA: Juvenile idiopathic arthritis, Dis: Disease, ons: Onset, No: Number, Jts: Joints,C-HAQ: Child health assessment questionnaire, MIO: Maximal interincisal opening, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, S: Serum, Syn. enhan: Synovial enhancement, MRI: Magnetic resonance imaging. A significant increase in serum S100A12 levels and total magnetic resonance imaging score in systemic and polyarticular subtypes compared to oligoarticular patients with juvenile idiopathic arthritis. NS: Not significant, S: Significant, HS: Highly significant

Table 6: Comparison between juvenile idiopathic arthritis patients with and without magnetic resonance imaging findings regarding demographic, clinical and laboratory data

Variables	+ve MRI No. = 16 Mean±SD	-ve MRI No. = 4 Mean±SD	t-value	p-value	Sig.
Age (years)	14.25±2.48	14.62±1.37	0.28	>0.05	NS
Age at disease onset (years)	9.09±2.80	10.0±3.36	0.55	>0.05	NS
Disease duration (years)	5.15±2.50	4.62±2.28	0.38	>0.05	NS
No. of active joints	4.50±2.38	4.18±1.60	0.31	>0.05	NS
Disease activity score	3.68±0.94	2.0±0.0	3.4	<0.05	S
C-HAQ	1.11±0.43	0.40±0.14	3.1	<0.05	S
Pain score	1.55±0.61	0.97±0.15	1.8	>0.05	NS
MIO (mm)	41.62±4.04	48.50±4.65	2.9	<0.05	S
ESR (mm h^{-1})	72.18±33.33	17.75±2.21	3.1	<0.05	S
CRP(mg mL^{-1})	25.62±9.64	6.75±0.95	3.8	<0.05	S
Serum S100A12 (ng mL^{-1})	781.56±346.45	203.75±117.71	3.2	<0.05	S

MRI: Magnetic resonance imaging, +ve: Positive, –ve: Negative, No: Number, C-HAQ: Child health assessment questionnaire, MIO: Maximal interincisal opening, A significant decrease in maximal interincisal opening and a significant increase in serum S100A12 levels among juvenile idiopathic arthritis patients with magnetic resonance imaging abnormalities in temporomandibular joints compared to those without magnetic resonance imaging findings. NS: Not significant, S: Significant, HS: Highly significant

older at disease onset than RF-ve JIA patients (t = 3.1, p<0.05). While the frequencies of TMJ involvement were 80 and 88.9% among polyarticular RF+ve and RF-ve patients, respectively.

Comparison between JIA patients with and without MRI findings: MRI abnormalities of TMJ have been detected in 16 JIA patients while 4 patients showed no MRI TMJ findings.

There was a significant increase in mean disease activity score, C-HAQ, ESR, CRP levels and serum S100A12 concentration, meanwhile; MIO showed a significant decrease among JIA patients with MRI findings when compared to those without MRI TMJ abnormalities. No significant difference between both groups was found regarding haemoglobin level or neutrophil count (p> 0.05) (Table 6).

Comparison between JIA patient with or without TMJ pain regarding MIO: A significant decrease in MIO has been detected among JIA patients with pain of TMJ at rest or on jaw movement (t = 2.6, p<0.05, t = 3.6, p<0.05), respectively when compared with patients who didn't complain of TMJ pain.

Association and correlation studies: Using Chi-square test: A significant association has been found between clinical signs of TMJ affection and contrast enhanced MRI TMJ abnormalities (12 patients have shown signs of TMJ affection by both clinical and contrast enhanced MRI examinations (χ^2 = 7.5, p<0.05), while this association was not detected regarding symptoms (χ^2 = 3.3, p>0.05) among JIA patients.

Serum levels of S100A12 showed a high significant positive correlation with disease activity score, pain score, ESR, CRP serum levels, synovial enhancement score (Fig. 5) and total MRI score (Table 7). No significant correlation was found between serum levels of S100A12 and neutrophil count in JIA patients (r = 0.03, p>0.05) (Fig. 6). A high significant positive correlation could be detected between total MRI score and disease activity score, C-HAQ, pain score by VAS, ESR, serum S100A12 concentrations and CRP levels. While MIO showed high significant negative correlations with disease activity score, C-HAQ, ESR, CRP levels, serum S100A12 concentration and total MRI score (Table 7).

Table 7: Correlation between serum S100A12 levels, magnetic resonance imaging parameters, maximal interincisal opening and different clinical, laboratory, magnetic resonance imaging data

Variables	Statistical values	DA score	C-HAQ	Pain score	MIO	ESR	CRP	SerumS100A12	Total MRI score
Serum S100A12	r	0.84	0.61	0.92	-0.76	0.94	0.83		0.79
	P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001		<0.001
	Sig.	HS	S	HS	HS	HS	HS		HS
Total MRI score	r	0.86	0.76	0.71	-0.82	0.84	0.89	0.79	
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	
	Sig.	HS	HS	HS	HS	HS	HS	HS	
Syn. enh. s.	r	0.83	0.71	0.63	-0.67	0.76	0.84	0.77	0.83
	p	<0.001	<0.001	<0.05	<0.05	<0.001	<0.001	<0.001	<0.001
	Sig.	HS	HS	S	S	HS	HS	HS	HS
Effusion s.	r	0.76	0.72	0.6	-0.85	0.71	0.79	0.66	0.82
	p	<0.001	<0.001	<0.05	<0.001	<0.001	<0.001	<0.05	<0.001
	Sig.	HS	HS	S	HS	HS	HS	S	HS
MIO	r	-0.82	-0.78	-0.7		-0.77	-0.84	-0.76	-0.82
	p	<0.001	<0.001	<0.05		<0.001	<0.001	<0.001	<0.001
	Sig.	HS	HS	S		HS	HS	HS	HS

HSDA: Disease activity, C-HAQ: Child health assessment questionnaire, MIO: Maximal interincisal opening, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, s.: score, MRI: magnetic resonance imaging, Syn.enh: synovial enhancement. A high significant positive correlation between serum S100A12 levels and total magnetic resonance imaging score. NS: Not significant, S: Significant, HS: Highly significant

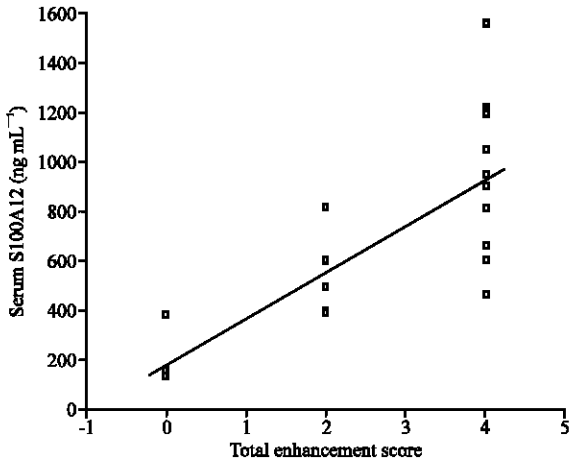

Fig. 5: Pearson correlation coefficient test. A high significant positive correlation between serum S100A12 levels and total synovial enhancement score in patients with juvenile idiopathic arthritis

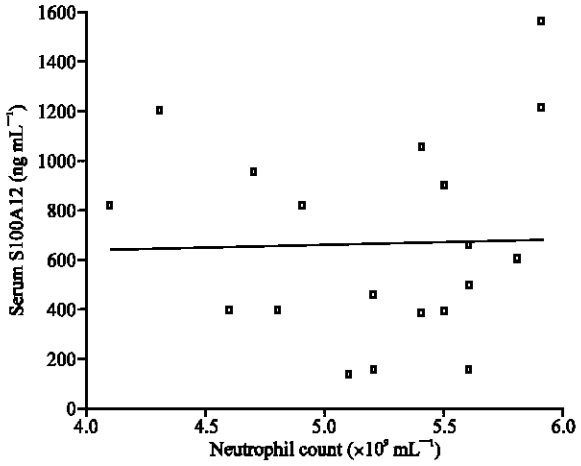

Fig. 6: Pearson correlation coefficient test. No significant correlation between serum S100A12 levels and neutrophil count in patients with juvenile idiopathic arthritis

Juvenile Idiopathic Arthritis (JIA) is one of the most common chronic diseases of childhood. Diagnosis is based on clinical observation of persistent arthritis in one or more joints for a minimum of six weeks, with onset prior to the age of sixteen years (Sawyer *et al*., 2005).

Lotze and Tracey (2005) reported that a novel group of important inflammatory molecules has been introduced to the concept of innate immunity. In parallel to Pathogen Associated Molecular Pattern (PAMP) as exogenous factors initiating inflammation. The term Damage Associated Molecular Pattern (DAMP) proteins for endogenous molecules that exhibit a double life as intracellular molecules which have a role in cell homeostasis e.g. calcium binding proteins or chromatin stabilizing molecules but after release into extracellular compartment as a result of cell damage or inflammation, they become danger signals that activate immune cells and vascular endothelium. Examples are heat shock proteins, uric acid and S100 proteins (Van Eden *et al*., 2005).

S100 A12 (calgranulin C) is a member of S100 family which are calcium binding proteins and has been described to define a novel pro-inflammatory axis by binding to the multiligand receptor for advanced glycation end products (RAGE). The S100A12 is expressed and secreted by activated neutrophilic granulocytes (Foell *et al*., 2003). Interaction of S100A12 with RAGE activates endothelial cells, macrophages and

lymphocytes, while blocking of RAGE in experimental models of arthritis leads to suppression of inflammatory response (Kim *et al*., 2005).

Grom and Hirsch (2000) revealed that S100A12 protein is released from neutrophils during interactions with activated endothelium. This study showed that serum S100A12 levels were highly significantly elevated in JIA patients compared to controls which were the same findings obtained by Foell *et al*. (2004). Similarly, Sunahori *et al*. (2006) detected high serum concentrations of S100A12 in patients with rheumatoid arthritis.

Wittkowski *et al*. (2008) reported that S100A12 is a useful marker protein for monitoring disease activity in several inflammatory diseases. Foell *et al*. (2004) detected that serum S100A12 levels were clearly elevated during active disease and that JIA patients without active inflammation had significantly lower S100A12 serum concentrations than did patients with active disease. This study is supported by them as serum levels of S100A12 were significantly elevated in patients with active disease compared to those without active JIA and a high significant positive correlation was found between serum levels of S100A12 and disease activity score among patients with JIA.

De Seny *et al*. (2008) found that serum concentrations of S100A12 were significantly correlated with variables that reflect disease activity of rheumatoid arthritis such as levels of CRP. The results of this study are in accordance with their study as serum levels of S100A12 showed high significant positive correlation with CRP levels for patients with JIA.

Foell *et al*. (2004) recorded that mean serum levels of S100A12 were significantly the highest among patients with systemic onset JIA followed by polyarticular then oligoarticular JIA. Yilmaz *et al*. (2001) concluded that systemic onset JIA is an aggressive disease with extensive activation of the immune system influenced by imbalance between proinflammatory cytokines and immune deactivators. This study is ongoing with them as serum levels of S100A12 were found to be significantly elevated among patients with systemic JIA then polyarticular followed by oligoarticular JIA. Frosch and Roth (2008) reported that the predominant role of the immune system in systemic JIA is underscored by the high expression and increased serum concentration of S100A12.

Foell and Roth (2004) noted that S100A12 is secreted during activation of neutrophilic granulocytes. The present study found no significant correlation between neutrophil count and serum levels of S100A12. Foell *et al*. (2004) suggested that high serum concentrations of S100A12 are not attributable to elevated numbers of circulating neutrophils as demonstrated by the lack of correlation to blood neutrophil count. Therefore, it may indicate the release of S100A12 by extra ordinarily activated neutrophils in systemic JIA. Jarvis *et al*. (2006) supported the hypothesis that there is fundamental activation abnormality of neutrophils in patients with polyarticular JIA.

Arthritis of TMJ in patients with JIA was recognized as early as 1897 (Ronchezel *et al*., 1995) but until recently it has been relatively ignored. Arthritis of TMJ is a concern, particularly in patients who are growing, because the mandibular growth plate is located below the fibrocartilage and therefore, is susceptible to damage from inflammation (Weiss *et al*., 2008).

The diagnosis of TMJ arthritis has increasingly been based on evidence obtained by imaging. Orthropantogram, ultrasonography and magnetic resonance imaging have all been used in evaluation and detection of TMJ arthritis (Jank *et al*., 2007).

Küseler *et al*. (2005) suggested that TMJ involvement may occur in many JIA cases with activity continuing for many years without presenting symptoms or clinical signs causing a delay in detection as they have found in their study that TMJ symptoms and signs were present in 8 and 13 patients with JIA, respectively. This study is supported by them as symptoms and signs of TMJ disease were detected among 8 and 12 patients, respectively. On the other hand, Müller *et al*. (2009) reported that signs of TMJ affection were detected in 73.3% of JIA patients. Their high percentage for signs than this study (60% of JIA patients) may be due that more patients had participated in their study.

Martini *et al*. (2001) demonstrated that clinical manifestations such as pain at rest, local morning stiffness, decreased mouth opening, pain during joint movement may point at TMJ involvement among patients with JIA.

Twilt *et al*. (2004) found that clinical symptoms were not reliable in detection of TMJ involvement in patients with JIA because they were not present in majority of cases as only 12% of children had complained of TMJ pain. In this study, TMJ pain at rest could be detected in 15% of patients with JIA.

This study showed that tenderness on palpation of TMJ and crepitations were present in 25 and 20% of cases, respectively. A finding which is supported by Jank *et al*. (2007), who reported a frequency of 22.9% for JIA patients with tenderness on TMJ palpation.

Among JIA patients in this study; 4 patients (20%) complained of pain on TMJ function while Argyropoulou *et al*. (2009) reported this symptom in only 2 JIA patients. On the other hand, Engström *et al*. (2007)

in his follow up study found that the frequency of pain on TMJ movement had increased to reach 29% of JIA cases. This may be due to that their patients had longer disease duration. Twilt *et al.* (2007) suggested that long disease duration is a risk factor for TMJ involvement.

Müller *et al.* (2009) revealed that 23.3% of their JIA patients had limited Maximal Interincisal Opening (MIO) which supports our results as the decrease in MIO could be detected in 25% of JIA patients in this study.

Pedersen *et al.* (2008) found in their study that maximal opening capacity of patients were at the lower range of normal but it was significantly decreased in JIA patients compared to controls. Our findings are consistent with them as the mean maximal opening capacity was highly significantly lower in patients with JIA compared to controls. It was also significantly lower among patients with systemic JIA than the polyarticular type and it was the highest among patients with oligoarticular disease. A finding which was confirmed by Arabshahi *et al.* (2005) as they have found that MIO was better among oligoarticular JIA patients than polyarticular type.

Billiau *et al.* (2007) revealed that restricted MIO was the most frequent clinical finding occurring in nearly one third of patients 33.3% and it was more frequent among JIA patients with long standing and active disease, they suggested that impaired function of the TMJ and surrounding muscles during activity explains the association with disease activity and possibly with severity. This study is ongoing with them as decreased MIO was one of the most frequent signs of TMJ involvement in patients with JIA (25% of cases) and it was significantly decreased for patients with active disease compared to those with no activity. Reduced MIO also showed high significant negative correlations with disease activity score and child health assessment questionnaire.

In the present study; JIA patients with TMJ pain showed a significant decrease of the mean MIO in comparison to patients without pain. Moreover, there was a significant negative correlation between reduced MIO and pain score. Arabshahi *et al.* (2005) agreed with this study, they have found that the mean MIO was lower in patients with TMJ pain than those without pain, they reported that this reflects pain limited movement.

The lack of symptoms and abnormalities on TMJ examination does not exclude the presence of TMJ disease, so radiological examination on regular basis is necessary (Twilt *et al.*, 2003; Weiss *et al.*, 2008). The MRI is considered the gold standard for the study of TMJ disease because it evaluates bone and depicts intraarticular fluid. Contrast enhanced MRI after injection of gadolinium demonstrates an inflammatory state in the joint (Pedersen *et al.*, 2008; Argyropoulou *et al.*, 2009).

In this study 80% of JIA cases showed TMJ affection using post-contrast MRI. Weiss *et al.* (2008) supported our results as they have recorded a frequency (75%) of TMJ arthritis using gadolinium enhanced MRI among their patients. They revealed that it is at the higher end of previously reported ranges 17-87% (Pedersen *et al.*, 2001; Twilt *et al.*, 2006) which indicates that TMJ is one of the most commonly involved joints in patients with JIA. While Twilt *et al.* (2004) detected TMJ abnormalities among 45% of patients with JIA diagnosed by orthopantogram. They said that the frequency of TMJ involvement depends on the radiographic tool used to find out TMJ disease. Küseler *et al.* (2005) suggested that contrast enhanced MRI may be an efficient method in diagnosing inflammatory changes in TMJ.

Küseler *et al.* (2005) reported that patients in their study were diagnosed to have JIA due to arthritis in joints other than the TMJ and they were surprised to see that the majority already had signs of TMJ involvement on MRI examinations. They detected synovial enhancement in 93%, erosions in 71% and pannus in 26% of TMJs. This study is ongoing with them regarding the high frequency of temporomandibular joints with synovial enhancement (75.5%) but it detected lower frequency of erosions (17.5%) and pannus (22.5%).

This study has detected effusion in 47.5% of TMJs among patients with JIA. On the contrary Arabshahi *et al.* (2005) showed a frequency of 57% for TMJ effusion using MRI. This may be due to that their patients were younger at disease onset than JIA patients in this study. Arabshahi and Cron (2006) suggested that younger age at disease onset is one of the causes of bad prognosis regarding TMJ. On the other hand, Argyropoulou *et al.* (2009) found that by MRI, effusion was present in only 10% of TMJs. While Küseler *et al.* (2005) supported this study as TMJ effusion was detected in 13 JIA patients in their and our studies.

Pedersen *et al.* (2001) suggested that TMJ abnormalities as detected by MRI are dependent on disease duration. The results of this study revealed that patients with TMJ MRI findings have longer disease duration than those without TMJ MRI signs although, the difference hasn't reached statistical significance.

Twilt *et al.* (2007) concluded that JIA disease activity and severity could be reflected in TMJ involvement. In addition, Twilt *et al.* (2008) reported that inactive disease state prevents TMJ abnormalities among patients with JIA and this needs institution of more aggressive therapy that will decrease disease activity. Argyropoulou *et al.* (2009) detected a significant association between abnormal MRI findings of TMJs and disease activity among patients with JIA. The present study is in

accordance with them as we have found a high significant increase in mean of synovial enhancement score and a significantly higher effusion, total MRI scores in JIA patients with active disease compared to those who were not in the active phase of the disease and our results have also showed a high significant positive correlation between total synovial enhancement, effusion and MRI scores with both disease activity, C-HAQ scores. On the contrary, Billiau *et al.* (2007) found no correlation between disease characteristics such as disease activity, disease duration on one hand and radiological manifestations of TMJ abnormalities in patients with JIA. This difference with our results may be due to that they have examined TMJs by orthopantogram while contrast enhanced MRI was the tool used to diagnose TMJ disease in this study.

Despite increased TMJ changes by MRI, little symptoms could be detected (Pedersen *et al.*, 2008) they suggested that symptoms under estimate the inflammatory state of TMJ among patients with JIA. On the other hand, Argyropoulou *et al.* (2009) reported that all patients with clinical signs on TMJ examination had TMJ disease on post contrast MRI assessment. This study is ongoing with them as we have detected a significant association between MRI findings and clinical signs of TMJ involvement while this association was not significant regarding symptoms. Küseler *et al.* (2005) proposed that clinical examination seems to be more reliable than asking for symptoms of TMJ affection, since, all patients showing findings by clinical examination also had pathological signs on post contrast MRI. So, it seems more reasonable to select patients without clinical findings for MRI examination. Our results are supported by Küseler *et al.* (2005) as this study have included 4 JIA patients without clinical signs of TMJ involvement but post contrast MRI studies showed TMJs abnormalities.

Pedersen *et al.* (2001) reported that the severity of TMJ involvement was more pronounced in systemic and polyarticular JIA. Arabshahi and Cron (2006) also noted that the worst out come for TMJ affection was detected in patients with systemic or polyarticular disease. The results of this study are ongoing with them as the total MRI score of TMJ abnormalities was significantly higher among patients with systemic followed by polyarticular then oligoarticular JIA. This may be explained by Wallace *et al.* (2005) opinion that patients with oligoarticular arthritis are more likely to have longer periods of inactive disease compared to the polyarticular type. Our results are supported by their opinion as disease activity score was significantly higher for children with systemic followed by polyarticular JIA while those with oligoarticular type showed inactive disease.

In this study, polyarticular RF positive patients showed a lower frequency of TMJ involvement 80% than the RF negative cases 88.9%. Twilt *et al.* (2004) in their study noted that, it is surprising that the frequency of TMJ arthritis within the polyarticular RF positive group which is known by it's erosive character had a low frequency of TMJ affection. They said that this may be due to that RF positive patients had late disease onset compared by others. They postulated that older age at disease onset may be associated with less manifestations.

Taylor *et al.* (1993) revealed that the mechanism of TMJ involvement in JIA is unknown but it is probably related to the presence of synovial inflammation. Martini *et al.* (2001) proposed that proinflammatory cytokines can cause abnormalities of TMJs in JIA. In addition, Twilt *et al.* (2004) suggested that the severity of TMJ involvement is directly related to inflammatory variables of JIA. S100A12 has been known to be involved in the process of communication between neutrophils and endothelium thus triggering adhesion and invasion of inflammatory cells. Thus, neutrophils represent an important cellular component that contributes to synovial inflammation (Wipke and Allen, 2001). This study is supported by them as we have found a high significant positive correlation between MRI total score of TMJs and serum S100 A12 (the proinflammatory protein) as well as CRP levels among JIA patients.

Küseler *et al.* (2005) reported that studies correlating changes of MRI results in joints other than the TMJ with histological findings have shown that enhancement of synovial membrane on using gadolinium enhanced MRI is related to synoival inflammation (Gaffney *et al.*, 1995). Animal studies of TMJ arthritis comparing histological findings with MRI support this conclusion. Data from murine models of arthritis demonstrated the ability of S100A12 to trigger synovial inflammation, in addition; blocking the interaction of S100A12 with its receptor RAGE has suppressed clinical and histological evidence of arthritis in mouse models (Schmidt *et al.*, 2001). This may explain the high significant positive correlation between total score of synovial enhancement on one hand and serum S100 A12 concentrations, CRP levels on the other hand, among JIA patients in this study. Müller *et al.* (2009) noted that the presence of synovial enhancement is an indicator of inflammation.

Küseler *et al.* (2005) recorded that contrast enhanced MRI is a helpful tool in detecting TMJ abnormalities. Pedersen *et al.* (2008) recommended clinical examination of children with JIA every 6 months. Once TMJ arthritis is discovered, the primary goal is to control synovitis by medications. Foell *et al.* (2004) suggested a functional role of S100A12 in JIA. Schmidt *et al.* (2001) reported that anti S100A12 antibodies revealed anti-inflammatory effects in

mouse models of arthritis. Twilt *et al.* (2004) noted that in conjunction with medical treatment, the basic principles in rheumatology such as: heat, cold therapy and exercises are needed to improve TMJ range of motion. Weiss *et al.* (2008) asked an important question, should a child with arthritis of 2 temporomandibular joints and 3 other joints with active disease be classified as polyarticular JIA.

CONCLUSIONS

TMJ arthritis could be detected in most cases of JIA using contrast enhanced MRI. The S100A12 may reflect neutrophil activation during synovial inflammation by the increase in it's serum levels in JIA patients. It may also point to synovial inflammation thorough it's significant correlations with synovial enhancement, effusion, total MRI and disease activity scores. Systemic and polyarticular JIA subtypes showed the worst results regarding S100A12 serum levels and MRI scores. Contrast enhanced MRI may be recommended in JIA patients especially those with no clinical signs of TMJ disease. Further studies on larger scale of JIA patients are needed for monitoring TMJ arthritis and for investigating the role of S100A12 in human arthritis as it may lead to a potential therapy that focuses on the pro-inflammatory activities of human S100A12.

REFERENCES

Agerberg, G., 1974. Maximal mandibular movements in children. Acta Odontol. Scand., 32: 147-159.

Arabshahi, B. and R.Q. Cron, 2006. Temporomandibular joint arthritis in juvenile idiopathic arthritis: The forgotten joint. Curr. Opin. Rheumatol., 18: 490-495.

Arabshahi, B., E.M. Dewitt, A.M. Cahill, R.D. Kaye, K.M. Baskin, R.B. Towbin and R.Q. Cron, 2005. Utility of corticosteroid injection for temporomandibular arthritis in children with juvenile idiopathic arthritis. Arthritis Rheum., 52: 3563-3569.

Argyropoulou, M.I., P.N. Margariti, A. Karali, L. Astrakas, S. Alfandaki, P. Kosta and A. Siamopoulou, 2009. Temporomandibular joint involvement in juvenile idiopathic arthritis: Clinical predictors of magnetic resonance imaging signs. Eur. Radiol., 19: 693-700.

Billiau, A.D., Y. Hu, A. Verdonck, C. Carels and C. Wouters, 2007. Temporomandibular joint arthritis in juvenile idiopathic arthritis: Prevalence, clinical and radiological signs and relation to dentofacial morphology. J. Rheumatol., 34: 1925-1933.

De Seny, D., M. Fillet, C. Ribbens, R. Marée and M.A. Meuwis *et al.*, 2008. Monomeric calgranulins measured by SLEDI-TOF mass spectrometry and calprotectin measured by ELISA as biomarkers in arthritis. Clin. Chem., 54: 1066-1075.

Engström, A.L., A. Wänman, A. Johansson, P. Keshishian and M. Forsberg, 2007. Juvenile arthritis and development of symptoms of temporomandibular disorders: A 15-year prospective cohort study. J. Orofac. Pain., 21: 120-126.

Foell, D., T. Kucharzik, M. Kraft, T. Vogl, C. Sorg, W. Domschke and J. Roth, 2003. Neutrophil derived S100 A12 (EN-RAGE) is strongly expressed during a chronic active inflammatory bowel disease. Gut, 52: 847-853.

Foell, D. and J. Roth, 2004. Proinflammatory S100 proteins in arthritis and autoimmune disease. Arthritis Rheum., 50: 3762-3771.

Foell, D., H. Wittkowski, I. Hammerschmidt, N. Wulffraat and H. Schmeling *et al.*, 2004. Monitoring neutrophil activation in juvenile rheumatoid arthritis by S100A12 serum concentrations. Arthritis Rheum, 50: 1286-1295.

Foell, D., H. Wittkowski, T. Vogl and J. Roth, 2007. S100 proteins expressed in phagocytes: A novel group of damage associated molecular pattern molecules. J. Leukoc. Biol., 81: 28-37.

Frosch, M. and J. Roth, 2008. New insights in systemic juvenile idiopathic arthritis from pathophysiology to treatment. Rheumatology, 47: 121-125.

Gaffney, K., J. Cookson, D. Blake, A. Coumbe and S. Blades, 1995. Quantification of rheumatoid synovitis by magnetic resonance imaging. Arthritis Rheum., 38: 1610-1617.

Graham, T.B., 2005. Imaging in juvenile arthritis. Curr. Opin. Rheumatol., 17: 574-578.

Grom, A.A. and R. Hirsch, 2000. T cell and T cell receptor abnormalities in the immunopathogenesis of juvenile rheumatoid arthritis. Curr. Opin. Rheumatol., 12: 420-424.

Jank, S., S. Haase, H. Strobl, H. Michels and R. Häfner *et al.*, 2007. Sonographic investigation of the temporomandibular joint in patients with juvenile idiopathic arthritis: A pilot study. Arthritis Rheum., 57: 213-218.

Jarvis, J.N., H.R. Petty, Y. Tang, M.B. Frank and P.A. Tessier *et al.*, 2006. Evidence for chronic peripheral activation of neutrophils in polyarticular juvenile rheumatoid arthritis. Arthritis Res. Ther., 8: R154-R154.

Kim, W., B.I. Hudson, B. Moser, J. Guo and L.L. Rong *et al*., 2005. Receptor for advanced glycation end products and its ligands: A journey from the complications of diabetes to its pathogenesis. Ann. N. Y. Acad. Sci., 1043: 553-556.

Küseler, A., T.K. Pedersen, J. Gelineck and T. Herlin, 2005. A 2 year follow up study of enhanced magnetic resonance imaging and clinical examination of the temporomandibular joint in children with juvenile idiopathic arthritis. J. Rheumatol., 32: 162-169.

Lotze, M. and K. Tracey, 2005. High mobility group box 1 protein (HMGB1): Nuclear weapon in the immune arsenal. Nat. Rev. Immunol., 5: 331-342.

Mantha, S., R. Thisted, J. Foss, J.E. Ellis and M.F. Roizen, 1993. A proposal to use confidence intervals for visual analog scale data for pain measurement to determine clinical significance. Anaesth. Analg., 77: 1041-1047.

Martini, G., U. Bacciliero, A. Tregnaghi, M.C. Montesco and F. Zulian, 2001. Isolated temporomandibular synovitis as unique presentation of juvenile idiopathic arthritis. J. Rheumatol., 28: 1689-1692.

Müller, L., C.J. Kellenberger, E. Cannizzaro, D. Ettlin and T. Schraner *et al*., 2009. Early diagnosis of temporomandibular joint involvement in juvenile idiopathic arthritis: A pilot study comparing clinical examination and ultrasound to magnetic resonance imaging. Rheumatology, 48: 680-685.

Pedersen, T.K., J.J. Jensen, B. Melsen and T. Herlin, 2001. Resorption of the temporomandibular condylar bone according to subtypes of juvenile chronic arthritis. J. Rheumatol., 28: 2109-2115.

Pedersen, T.K., A. Küseler, J. Gelineck and T. Herlin, 2008. A prospective study of magnetic resonance and radiographic imaging in relation to symptoms and clinical findings of the temporomandibular joint in children with juvenile idiopathic arthritis. J. Rheumatol., 35: 1668-1675.

Petty, R.E., T.R. Southwood, P. Manners, J. Baum and D.N. Glass *et al*., 2004. The International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: Second revision, Edmonton 2001. J. Rheumatol., 31: 390-392.

Pietzch, J. and S. Hoppmann, 2009. Human S100A12: A novel key player in inflammation Amino Acids, 36: 381-389.

Ronchezel, M.V., M.O. Hilário, J. Goldenberg, H.M. Lederman, K. Jr. Faltin, M.F. de Azevedo and C.K. Naspitz, 1995. Temporomandibular joint and mandibular growth alterations in patients with juvenile rheumatoid arthritis. J. Rheumatol., 22: 1956-191.

Sawyer, M.G., J.A. Carbone, J.N. Whitham, D.M. Roberton, J.E. Taplin, J.W. Varni and P.A. Baghurst, 2005. The relation between health related quality of life, pain and coping strategies in juvenile arthritis–A one year prospective study. Qual. Life Res., 14: 1585-1598.

Schmidt, A.M., S.D. Yan, S.F. Yan and D.M. Stern, 2001. The multi ligand receptor RAGE as a progression factor amplifying immune and inflammatory responses. J. Clin. Invest., 108: 949-95.

Singh, G., B.H. Athreya, J.F. Fries and D.P. Goldsmith, 1994. Measurement of health status in chidren with juvenile rheumatoid arthritis. Arthritis Rheum., 37: 1761-1769.

Sunahori, K., M. Yamamura, J. Yamana, K. Takasugi, M. Kawashima and H. Makino, 2006. Increased expression of receptor for advanced glycation end products by synovial tissue macrophages in rheumatoid arthritis. Arthritis Rheum., 54: 97-104.

Taylor, D.B., P. Babyn, S. Blaser, S. Smith and A. Shore *et al*., 1993. MR evaluation of the temporomandibular joint in juvenile rheumatoid arthritis. J.Comp. Assist. Tomog., 17: 449-454.

Tselepis, A.D., M. Elisaf, S. Besis, S.A. Karabina, M.J. Chapman and A. Siamopoulou, 1999. Association of the inflammatory state in active juvenile rheumatoid arthritis with hypo-high density lipoproteinemia and reduced lipoprotein-associated platelet activating factor acetyl hydrolase activity. Arthritis Rheumatol., 42: 373-383.

Twilt, M., E. van der Giesen, S.M. Mobers, R. ten Cate and L.W. van Suijlekom-Smit, 2003. Abrupt condylar destruction of the mandibula in juvenile idiopathic arthritis. Ann. Rheum. Dis., 62: 366-367.

Twilt, M., S.M. Mobers, L.R. Arends, R. ten Cate and L. van Suijlekom-Smit, 2004. Temporomandibular involvement in juvenile idiopathic arthritis. J. Rheumatol., 31: 1418-1422.

Twilt, M., A.J. Schulten, P. Nicolaas, A. Dülger and L.W. van Suijlekom-Smit, 2006. Facioskeletal changes in children with juvenile idiopathic arthritis. Ann. Rheum. Dis., 65: 823-825.

Twilt, M., L.R. Arends, R.T. Cate and L.W. van Suijlekom-Smit, 2007. Incidence of temporomandibular involvement in juvenile idiopathic arthritis. Scand. J. Rheumatol., 36: 184-188.

Twilt, M., A.J. Schulten, F. Verschure, L. Wisse, B. Prahl-Andersen and L.W. van Suijlekom-Smit, 2008. Long term follow up of temporomandibular joint involvement in juvenile idiopathic arthritis. Arthritis Rheum., 59: 546-552.

Van Eden, W., R. van der Zee and B. Prakken, 2005. Heat shock proteins induce T-cell regulation of chronic inflammation. Nat. Rev. Immunol., 5: 318-33.

Viola, S., E. Felici, S. Magni-Manzoni, A. Pistorio and A. Buoncompagni *et al*., 2005. Development and validation of a clinical index for assessment of long term damage in juvenile idiopathic arthritis. Arthritis Rheum., 52: 2092-2102.

Wallace, C.A., N. Ruperto and E. Giannini, 2004. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J. Rheumatol., 31: 2290-2294.

Wallace, C.A., B. Huang, M. Bandeira, A. Ravelli and E.H. Giannini, 2005. Patterns of clinical remission in select categories of juvenile idiopathic arthritis. Arthritis Rheum., 52: 3554-3562.

Weiss, P.F., B. Arabshahi, A. Johnson, L.T. Bilaniuk and D. Zarnow *et al*., 2008. High prevalence of temporomandibular joint arthritis at disease onset in children with juvenile idiopathic arthritis, as detected by magnetic resonance imaging but not by ultrasound. Arthritis Rheum., 58: 1189-1196.

Wipke, B.T. and P.M. Allen, 2001. Essential role of neutrophils in the initiation and progression of a murine model of rheumatoid arthritis. J. Immunol., 167: 1601-1608.

Wittkowski, H., M. Frosch, N. Wulffraat, R. Goldbach-Mansky and T. Kallinich *et al*., 2008. S100A12 is a novel molecular marker differentiating systemic–onset juvenile idiopathic arthritis from other causes of fever of unknown origin. Arthritis Rheum., 58: 3924-3931.

Yilmaz, M., S.G. Kendirli, D. Altintas, G. Bingöl and B. Antmen, 2001. Cytokine levels in serum of patients with juvenile rheumatoid arthritis. Clin. Rheumatol., 20: 30-35.