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Different Patterns of Juvenile Idiopathic Arthritis in Zagazig University Hospitals

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ABSTRACT

Background: Pediatric rheumatic diseases can cause considerable disease burden to children and their families. They are associated with the potential for physical disability, diminished quality of life and significant direct and indirect costs. **Objective:** We aimed to describe the clinical spectrum and the frequencies and different patterns of Juvenile idiopathic arthritis (JIA) in children in Zagazig University Hospitals.

Patients and methods: A cross-sectional study included 68 cases with Juvenile idiopathic arthritis < 16 years. The study was conducted over two years from December 2017 to December 2019. Investigations as complete blood count, C reactive protein, antinuclear antibody (ANA), rheumatoid factor (RF), complement C3 & C4, creatine phosphokinase, and EMG. Management and treatment plans were achieved and data about the results were collected.

Results: Most of patients diagnosed with rheumatological diseases were females. Oligoarticular JIA was the commonest subtype of JIA in our study followed by polyarticular then systemic onset type. NSAIDs was the commonest drug used by JIA patients followed by methotrexate then corticosteroids.

Conclusion: Early diagnosis and effective management of these children is essential so that they can lead a normal or near normal life especially in patients with rheumatological diseases with chronic morbidity as JIA.

Keywords: Juvenile idiopathic arthritis, Pediatric rheumatic diseases.

INTRODUCTION

Rheumatic diseases include many types such as, juvenile idiopathic arthritis, juvenile systemic lupus erythematosus, juvenile dermatomyositis, mixed connective tissue disease, Kawasaki disease, juvenile scleroderma and fibromyalgia [(1)]. Juvenile idiopathic arthritis (JIA), also known as juvenile rheumatoid arthritis, is the most common chronic systemic inflammatory disease in children below 16 years old of unknown etiology. It causes persistent joint pain, swelling and stiffness. Some children may experience symptoms for only a few months, while others have symptoms for the rest of their lives [(2)].

Pediatric rheumatic diseases (PRDs) are any of a variety of disorders marked by inflammation, degeneration, or metabolic derangement of the connective tissue structures especially the joints and related structures in children. Approximately 1 in 1000 children suffers from childhood rheumatic diseases [(3)]. Although they share many common symptoms, like pain, joint swelling, redness and warmth, they are distinct and each has its own special concerns and symptoms. Some pediatric rheumatic diseases affect the musculoskeletal system, but joint symptoms may be minor or nonexistent component. Pediatric rheumatic diseases can involve the eyes, skin, muscles and gastrointestinal tract as well [(4)].

We aimed to describe the clinical spectrum and the frequencies and different patterns of Juvenile idiopathic arthritis (JIA) in children in Zagazig University Hospitals.

PATIENTS AND METHOD

This study was a cross-sectional study carried out in Pediatrics and Rheumatology Departments of Zagazig University Hospitals. The study included 68 cases diagnosed with Juvenile idiopathic arthritis either inpatient or outpatient <16 years. The study was conducted over two years from December 2017 to December 2019.

Data were collected from all patients as follows:

1- Full history taking and duration of symptoms.
2- Full clinical examination including the skin, mucous membrane, cardiopulmonary auscultation and assessment of enlarged organs and glands. After performing the complete general examination, examination of the joints was done. Examination of the joint finally confirms the diagnostic impression suggested by the medical history (presence of arthritis or other finding and the type whether oligoarthritis or polyarthritis) [(5)].
3- Investigations as complete blood count.C- reactive protein, antinuclear antibody (ANA) profile, rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies, complement C3 & C4, creatine phosphokinase and EMG.
4-Treatment: Corticosteroids, nonsteroidal anti-inflammatory drugs include aspirin, ibuprofen, acetaminophen, disease-modifying antirheumatic drugs (DMARDS) including hydroxychloroquine, penicillamine, sulfasalazine, methotrexate, immunosuppressant drugs like cyclophosphamide, antidepressants like imipramine and new drugs such as tumor necrosis factor (TNF) blockers etanercept, adalimumab and infliximab.

Ethical approval:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written

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consent for acceptance of the operation. This work has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 20. Quantitative and categorical variables were used. Chi square test and Fisher exact test were done when appropriate. Kolmogorov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests were used to verify assumptions for use in parametric tests. One way ANOVA test (used with normally distributed data) and Kruskal Wallis test were used to compare more than two groups. The statistical significance level was set at 5% ($P \leq 0.05$). Highly significant difference was present if $p \leq 0.001$.

RESULTS

About 65% of the studied patients were females. Their ages ranged from 2 to 16 years with a mean of 11.04 years. Table (1) showed types of Juvenile idiopathic arthritis in details.

There was statistically non-significant difference between JIA patients as regards gender, age or diagnosis lag (**Table 2)**.

There was statistically non-significant difference between JIA patients regarding organomegaly, arthritis, or enlarged lymph node. There was statistically significant difference between JIA patients regarding fever (only in systemic JIA) and skin manifestations (higher in systemic JIA) (Table 3).

Table (4) showed that there was statistically non-significant difference between JIA patients regarding presence of positive ANA or rheumatoid factor. There was significant difference between them regarding presence of leukocytosis, anemia, thrombocytosis, elevated ESR (higher in patients with systemic JIA), and abnormal CRP (lower percentage of it in patients with systemic JIA).

There was statistically non-significant difference between JIA patients regarding use of biological therapy or hydroxychloroquine. There was statistically significant difference between them regarding use of NSAIDs, corticosteroids, sulphasalazine and methotrexate (Table 5).

Table (1): Distribution of the studied patients according to provisional diagnosis

Type of Juvenile idiopathic arthritis	N=68	%
• JIA polyarticular	19	15.8%
• JIA oligoarticular	25	20.8%
• Systemic onset JIA	13	10.8%
• Ankylosing spondylitis (AS)	10	8.3%
• Psoriatic arthritis	1	0.8%

Table (2): Comparison between different types of JIA patients regarding demographic characteristics

	Diagnosis					
	Poly	**Oligo**	**Systemic**	**Ankylosing spondylitis**	**Psoriatic arthritis**	**P**
	N=19 (27.9%)	**N=25 (36.8%)**	**N=13 (19.1%)**	**N=10 (14.7%)**	**N=1 (1.5%)**	
Gender:						
Female	10 (52.6)	20 (80)	8 (61.5)	5 (50)	1 (100)	0.25
Male	9 (47.4)	5 (20)	5 (38.5)	5 (50)	0 (0)	
Age (years)						
Mean ± SD	12.47 ± 2.59	10.64 ± 4.39	9.15 ± 3.74	12.2 ± 2.74	7	0.069
Range	7 – 16	2 – 16	2 – 13	8 – 15	7	
Diagnosis lag (days):						
Mean ± SD	7.58 ± 11.41	5.88 ± 4.49	3.15 ± 1.07	4.5 ± 2.95	2	0.64

F One Way ANOVA KW Kruskal Wallis test χ^2 Chi square test [1,3] the difference is significant between groups of polyarticular and systemic JIA.

Table (3): Comparison between different types of JIA patients concerning clinical presentation

	Group					
	Poly	**Oligo**	**Systemic**	**Ankylosing spondylitis**	**Psoriatic arthritis**	**P**
	N=19(%)	**N=25(%)**	**N=13(%)**	**N=10 (%)**	**N=1 (%)**	
Arthritis:	19 (100)	25 (100)	13 (100)	10 (100)	1 (100)	>0.999
Skin manifestations	0 (0)	0 (0)	3 (23.1)	1 (10)	1 (100)	0.002*
Organomegaly	0 (0)	1 (4)	1 (7.7)	0 (0)	0 (0)	0.702
Enlarged lymph node	0 (0)	0 (0)	2 (15.4)	0 (0)	0 (0)	0.083
Fever	0 (0)	0 (0)	13 (100)	0 (0)	0 (0)	0.002*

χ^2 Chi square test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

Table (4): Comparison between different types of JIA patients concerning laboratory data

	Group					p
	Poly	Oligo	Systemic	Ankylosing spondylitis	Psoriatic arthritis	
	N=19(%)	N=25(%)	N=13(%)	N=10 (%)	N=1 (%)	
Leucocytosis	0 (0)	0(0)	5 (38.5)	0 (0)	0 (0)	<0.001**
Anemia	0 (0)	1 (4)	8 (61.5)	0 (0)	0 (0)	<0.001**
Thrombocytosis	1 (5.3)	1 (4)	5 (38.5)	0 (0)	0 (0)	0.001**
Elevated ESR	1 (5.3)	1 (4)	10 (76.9)	0 (0)	0 (0)	<0.001**
Abnormal CRP	19 (100)	25 (100)	5 (38.5)	10 (100)	1 (100)	<0.001**
Positive ANA	3 (15.8)	2 (8)	0 (0)	0 (0)	0 (0)	0.361
Positive RF	2 (10.5)	4 (16)	1 (7.7)	0 (0)	0 (0)	0.655

χ^2 Chi square test *p < 0.05 is statistically significant **p ≤ 0.001 is statistically highly significant

Table (5): Comparison between different types of JIA patients concerning treatment used

	Group					P
	Polyarticular	oligoarticular	Systemic onset	Ankylosing spondylitis	Psoriatic arthritis	
	N=19(%)	N=25(%)	N=13(%)	N=10 (%)	N=1 (%)	
NSAIDs	18 (94.7)	22(88)	4 (30.8)	10 (100)	1 (100)	<0.001**
Corticosteroids	11 (57.9)	7 (28)	13 (100)	2 (20)	0 (0)	<0.001**
Methotrexate	13(68.4)	15(60)	12(92.3)	1(10)	0(0)	<0.001**
Biological therapy	1 (5.3)	1 (4)	3 (23)	2 (20)	0 (0)	0.284
Hydroxychloroquine	10 (52.6)	6 (24)	3 (23)	1 (10)	0 (0)	0.1
Sulphasalazine	1 (5.3)	4 (16)	0 (0)	10 (100)	0 (0)	<0.001**

χ^2 Chi square test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

DISCUSSION

Our study included 68 rheumatological juvenile idiopathic arthritis patients with the following subtypes: Oligoarticular (36.8%), polyarticular (27.9%), systemic onset (19.1%), ankylosing spondylitis (14.7%) and psoriatic arthritis (1.5%). This matches with the results of **Cassidy *et al.*** [6] who stated that oligoarthritis accounts for 50% to 80% of all children with JIA in Caucasian populations but mismatches with **Khubchandani and Hasija** [7] who found that systemic onset (SJIA) was the most common type of JIA and mismatches with **Olaosebikan *et al.*** [8] in Nigeria where polyarticular JIA was the most frequent type of JIA. This difference could be attributed to the attitude of dealing with most cases of oligo- and polyarticular JIA as outpatients while patients with SJIA usually referred or admitted because of their vague presentation [9].

In JIA, forty four patients were females (64.7%). Age ranged from 2 to 16 years with diagnosis lag ranged from 1 to 48 months. Females' predominance was evident in all types of JIA except for ankylosing spondylitis where males and females were equal. This matches with **Cassidy *et al.*** [6] who found that females are more common in oligoarticular and polyarticular JIA, but mismatches with our result in patients with systemic onset disease in which males and females were equal.

In comparing the statistical results between different types of JIA, we found statistically non-significant difference between the studied groups in gender, age or diagnosis lag. According to our results the main clinical manifestations in JIA patients were arthritis in 100% of patients, some had skin manifestations, organomegaly, fever and lymph node enlargement. In comparing the results of the five groups, there was statistically non-significant difference between the studied groups regarding organomegaly, skin manifestations, or enlarged lymph node. However, there was statistically significant difference between the studied groups regarding fever (only in systemic JIA) and skin manifestations (higher in systemic JIA). Among our 13 patients diagnosed with systemic onset JIA who represented 19.1% of total JIA cases, 100 % of patients had fever, 23.1 % had skin rash, 15.4% had generalized lymphadenopathy and 7.7% had organomegaly. Our results are near to **Petty *et al.*** [10] who found that systemic arthritis accounts for 5–15% of all cases of JIA seen in Western countries and to **Abdwani *et al.*** [11] who found that extra-articular features of JIA were predominately seen in patients with systemic onset JIA.

The lab results in JIA patients showed that about 7.4% had leukocytosis, 13.2% had anemia, 10.3% had thrombocytosis and 17.6% had elevated ESR. 88.3% of patients had abnormal CRP, 7.4% had positive ANA and 10.3% had positive rheumatoid factor. In comparing the lab results of the five types there was statistically non-significant difference between the studied groups regarding presence of positive ANA or rheumatoid factor. There was significant difference

between them regarding presence of leukocytosis, anemia, thrombocytosis, elevated ESR (higher in patients with systemic JIA), and abnormal CRP (lower percentage of it in patients with systemic JIA). This matches the results of **Cassidy *et al.*** [12] and **Wu *et al.*** [13] who found that anemia, leukocytosis and thrombocytosis were significantly found in systemic onset disease.

Rheumatoid factor was positive in 7 (10.29%) of all JIA patients, among which, two patients with polyarticular type (28.6%) and four patients with oligoarticular type (57.1%) and one patient with systemic onset type (14.3%). This is in agreement with **Naz *et al.*** [14] who reported that rheumatoid factor (RF) was positive in 10.27% of patients but out of all sero-positive patients, 95% were in polyarticular JIA and none of the patients with systemic onset disease were RF positive. While, in our study most of seropositive patients were oligoarticular type. Some studies from India by **Aggarwal *et al.*** [15] and from the West by **Ringold *et al.*** [16] showed very high seropositivity with polyarticular JIA.

ANA was positive in 5 (7.4%) of JIA patients and there was statistically non-significant difference between the studied groups regarding presence of positive ANA. This mismatches with the results of **Nigrovic *et al.*** [17] who found that ANA was detected in about 70% to 80% of oligoarticular type and constituted a risk factor for iridocyclitis. In our study only 2 patients with oligoarticular type (8%) had positive ANA.

Regarding treatment of our cases, about 80% had NSAIDs, 60.3% received methotrexate, 48.5%% received steroid, 29.4% received hydroxychloroquine, 22% received sulphasalazine and10.3% received biological therapy. Our results match with **Abdwani *et al.*** [11] who found that treatment modalities used for these patients included nonsteroidal anti-inflammatory drugs 97%, prednisolone 74%, methotrexate 61% and biologic agents 34%.

In comparing treatment in the five groups, there was statistically non-significant difference between the studied groups regarding use of biological therapy or hydroxychloroquine. However, there was significant difference between them regarding use of NSAIDs, corticosteroids, methotrexate and sulphasalazine with higher use of NSAIDs in ankylosing spondylitis, poly then oligoarticular JIA, and higher use of corticosteroid in systemic onset, followed by poly and oligoarticular. Methotrexate use was higher in systemic onset followed by poly then oligoarticular. In our study, 7 patients of JIA representing 10.3% received biological therapy most of them were of the systemic onset type and this matches with the result of **Al-Hemairi*et al.*** [18] who found that most of JIA patients who received biological therapy were of the systemic onset type.

We had 10 patients with AS represented 14.7% of JIA cases and 8.3% of all cases. 64.7% of the studied patients were females. Age ranged from 8 to 15 years. Diagnosis lag of the studied patients ranged from 2 to 12 months. This is in agreement with **Stone *et al.*** [19] who found that there was no difference in sex distribution between the groups and mismatches with **Sieper *et al.*** [20] who found that males are predominant 60% more than females.

In cases of juvenile-onset AS, treatment decisions were based on clinical experience rather than on evidence from clinical trials [21]. In treatment of our cases, all patients received NSAIDs and sulphasalazine. This matches with **Burgos-Vargas *et al.*** [22] who stated that NSAIDs might be helpful to a degree, especially if there is inflammatory back pain or peripheral arthritis and sulfasalazine can work well for peripheral arthritis, but it is not as effective for axial disease. 20% of our patients had corticosteroids and 10% received methotrexate**.** This matches with **Miroslav *et al.*** [23] who stated that methotrexate as second line agent is a good option in other forms of JIA. However, its use in juvenile AS is limited. Steroids are used sparingly, mostly as intra-articular injections with triamcionolone hexacetonide.

In the end, we recommend for increase of the value and proper use of different serological tests in diagnosis and follow up of rheumatological diseases. Expanded use of genetic diagnosis in different rheumatological diseases and using slit lamp examination should be done for patients of oligoarticular JIA especially ANA-positive for early detection of iridocyclitis. Regular follow up is important to ensure proper use of drugs and for early detection of complications of diseases and side effects of drugs.

CONCLUSION

The rheumatological diseases in pediatric population are under estimated and there is many overlap in diagnosis and it is less clear than adult-onset resulting in diagnostic lag in some patients. Early diagnosis and effective management of these children is essential so that they can lead a normal or near normal life especially in patients with rheumatological diseases with chronic morbidity as JIA.

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