Original article

The pattern of juvenile idiopathic arthritis; a retrospective Egyptian study

Background: *Juvenile idiopathic arthritis (JIA) is the most common autoimmune musculoskeletal disease in children. The spectrum of patients' profile of JIA showed many similarities and differences among different populations. Therefore, our study aimed to analyze the clinical data, laboratory data, treatment protocols and patient's outcomes of JIA among Egyptian population.* ***Methods:*** *We checked and analyzed medical files of children with JIA followed up at pediatric rheumatology clinic between 2004-2010 at Alexandria Main Children Hospital.* ***Results:*** *Our study included data about 63 Egyptian JIA patients (33 males and 30 females), with a mean age of 7.3±3.1 years (range 3-16 years). We found that oligoarticular subtype was the predominant (41.2%) among cases followed by polyarticular (35%) then systemic onset type in (23.8%). Most of the patients lived in rural areas (57.1%). Clinically, knee joints (74.6%) were the most affected joints while pallor (42.9%) was main extra-articular manifestations (42.2%) among all subtypes. Uveitis (6.3%) manifested among oligoarticular and polyarticular subtypes only. Rheumatoid factor and anti-nuclear antibody (ANA) were positive among 69.8% and 20.6% of the studied cases respectively. Remission rate was 47.6% and occurred mostly in oligoarticular subtype. Also, the regimen of combination of two drugs showed the highest remission rate (39.8%).* ***Conclusion:*** *The pattern of JIA among Egyptian children showed predominance of oligoarticular subtype specially at rural areas which differed from Western and Gulf countries pattern.*

Keywords: Juvenile idiopathic arthritis, oligoarticular, Rheumatoid factor, morning stiffness.

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children.[1, 2] It can be a serious and disabling condition complicated by joints destruction, growth disturbance, limb length discrepancy, osteoporosis and psychosocial problems.[3] Juvenile idiopathic arthritis is not a single disease, but a term that encompasses all forms of arthritis that begins before 16 years and persists for more than 6 weeks, and is of unknown origin.[1, 2] It is thought to have both genetic and environmental components, triggering inflammation through immune-dysregulation which is associated with alterations in both humoral and cell mediated immunity. T lymphocytes have a central role, releasing pro-inflammatory cytokines (e.g., TNF-α, IL-6, and IL-1)[4,5]. It has heterogeneous presentation therefore, the International League of Associations for Rheumatology (ILAR) proposed different classification.[3,6,7] The diagnosis of JIA is based upon the pattern of symptoms; morning stiffness (>1 hour), distribution of the inflamed joints and blood and x-ray findings and exclusion of other causes. While, the management of the disease is a multidisciplinary which rely on

anti-inflammatory and immune modulatory medications with physical therapy.[3,8] The incidence, prevalence, clinical presentations vary among ethnic and geographically different population. Few Egyptian studies described the clinical profile of affected children which was our motivation to conduct this study in order to evaluate the clinical patterns of JIA, laboratory parameters and outcome of different therapeutic regimens at Alexandria governorate.

METHODS

This is an observational retrospective cross-sectional study carried out at Alexandria University Children's hospital, Alexandria, Egypt. The current study was approved by local ethical committee of pediatric department and by the University Research Ethics Committee. All the medical records of the diagnosed JIA cases from January 2004 till December 2010 were checked. The cases were diagnosed according to ILAR criteria and they were followed up more than 6 months at Rheumatology Clinic.[6,7]

The collected data included: gender, age, age of first presentation, duration, clinical subtype (systemic onset arthritis, oligoarthritis or polyarthritis and arthralgia). The distribution of involved joints, main presenting features (morning stiffness, intermittent fever, skin rash, pallor, lymphadenopathy, hepato-splenomegaly, uveitis, pericardial effusion or valve damage). Results of laboratory data of CBC, CPR, erythrocyte sedimentation rate, rheumatoid factor (RF), antinuclear antibody (ANA). Results of Slit lamp examinations, chest x ray and echocardiography. Also, the study assessed different therapeutic protocols including: Single drug regimen (Prednisone, methotrexate or naproxen), double regimen (methotrexate with any of the previous drugs) and triple regimen as well as the outcome of disease whether remittent or unremittent. The disease course was considered remittent if disease activity lasted less than 2 years from the onset and terminated in remission without recurrence, while progressive or unremitting disease course was characterized by active disease for more than two years.[9]

Pilot study:

A pilot study was conducted. in order to fulfill the pilot study, a sample of 5 files of cases was chosen randomly. From the pilot study, the following points have been raised:

a. The Pediatric Rheumatology Clinic of the Children's Hospital, Alexandria University, was a suitable place for the research.

b. The researcher can carry out data collection skillfully and with confidence.

Analysis of data:

The results were checked. Then, the data were entered into SPSS system files (SPSS package version 18) and the following statistical measures were used: Descriptive statistics, Kolmogorov-Smirnov test, Kruskal Wallis test. Moreover, Chi-Square test, Fisher's Exact test and Monte Carlo test were used to test for significance among qualitative variables. The significance of the results was at the 5% level of significance.

Statistical analysis

Data was analyzed using the Statistical Program for Social Science (SPSS) version 18.0. Quantitative data was expressed as mean± standard deviation (SD). Qualitative data was expressed as frequency and percentage. Chi-square (X^2) test was used to compare the proportions between two qualitative parameters. Independent-samples t-test was used to compare between two means. P-value of <0.05 was considered significant.

RESULTS

The current study included 63 patients with mean age of 7.3 y ±3.1 (ranged from 3.8y to 16 y) at study time however, the mean age at diagnosis was 6.1±2.8 (ranged between 3 y and 14 y). About 57.1% of the cases were from rural areas (mostly oligoarticular subtype) while 42.9% were from urban areas with highly significant differences to rural areas (p=0.018). Positive family history of JIA was reported among 30.2% of cases as summarized in table (1).

Table (2) showed the spectrum of clinical patterns of JIA in our study in which oligoarticular subtype were the predominant (41.2%) followed by polyarticular (35%) then systemic onset type in (23.8%) with no other subtypes. In oligoarticular onset JIA, 2 subtypes were detected, persistent oligoarticular arthritis, which was present in 77.0 % and extended oligoarticular arthritis which occurred in 33% of cases.

The current study included 33 males and 30 females, at 1.1:1 ratio. However, there was a female predominance in the oligoarticular (57.7%) and the systemic onset subtypes (53,4%) in comparison to polyarthritis which showed male predominance (68%) but with no significant difference. (tables 1, 2)

Table (3) showed the distribution of involved joints in different subtypes. Knee joint was the most frequently affected in oligoarticular subtype (84.3%) while wrist (86.4%) and ankle were mostly

encountered in the polyarticular and systemic onset respectively. The results showed highly significant difference between the studied subtypes as regards affection of the wrist joint (p=0.011), the elbow joint (p=<0.0001), cervical joint (p=0.001), sacroiliac joint (0.002), MTPS (p=0.014), PIPS (p=0.0002) and MCPS (p=<0.0001) in polyarticular type when compared to other subtypes. Meanwhile, no statistically significant differences in affection of the knee, the ankle, the hip and the shoulder joints between the subtypes.

Regarding the clinical characteristics of children, table (3, 4) summarized that as it revealed highly significant difference between the studied subtypes as regards the intermittent fever (p=<0.0001), skin rash (p=<0.0001), lymphadenopathy (p=0.008), hepatosplenomegaly (p=0.008) and cardiac involvement (valve damage or pericardial effusion) (p=0.001) to systemic onset JIA rather than the other subtypes. While, the results showed no statistically significant differences regarding morning stiffness, pallor, uveitis, pleuritic, renal, skin, GIT involvements, oral and CNS disease between the three studied subtypes.

Table (5) presented the results of main laboratory investigations. Anemia, leukocytosis, thrombocytopenia, elevated first hour ESR, and CRP were common finding at presentation but without significant difference among the subgroups. The results detected that the difference in raised second hour of ESR was significant high (p=0.018) in polyarticular type when compared to others. Also, difference in the percent of positive RF cases and ANA positive cases ((p=0.0001, p=0.007) were significantly higher in oligoarticular type.

The difference in the percent of cases with positive RF was statistically significant higher among unremitting groups when compared to remitting group (p = 0.003). Meanwhile our results showed no statistically differences between remitting and unremitting groups as regards number of ANA positive cases as in table (6).

Lastly, the outcome of the disease was displayed at table (1). In general, disease remission was achieved among 30 cases out of 63 (47.4%) which were mostly (46.3%) among persistent oligoarthritis. Table (7) summarized the relation of remission to the drug regimen as it revealed that the difference in percent of remittent cases who were on tow drug regimen was statistical a significant higher (P=0.035*) when compared to single drug users (53.6% versus 20.1%). However, no significant difference between remitted cases on double and triple therapy.

Table 1. General characteristics of children with JIA according to the onset type.

	Total N=63	**SO-JIA N=15**	**Oligo-JIA N=26**	**Po-JIA N=22**	**Test of significance.**
Gender					
Male	33 (52.4%)	7(46.6%)	11(42.3%)	15(68%)	X^2=3.46 P=0.178
Female	30 (47.6%)	8(53.4%)	15(57.7%)	7(32%)	
Age (years)					
Range	3.8-16	4-16	3-14	3-14	$^{KW}X^2$=2.694 P=0.26
Mean ± SD	7.3±3.1	6.9 ±2.9	11.13± 6.1	7.9±3.1	
Age at disease onset (years)					
Range	3-14	3-14	3-12	3-12	$^{KW}X^2$=2.16 P=0.34
Mean ± SD	6.1±2.8	5.6±2.6	6.0±2.9	6.6±2.8	
Residence					
Urban	27(42.9%)	10 (66.7%)	6 (23.0%)	11(50.0%)	X^2=8.08 P = 0.018*
Rural	36 (57.1%)	5(33.3%)	20 (77.0%)	11(50.0%)	
Family history of JIA	19(30.2)	2 (13.3)	10(38.5)	7 (31.8)	X^2 = 2.896 P = 0.408

X^2: Chi-square test $^{KW}X^2$: K*: Statistically significant at $p \leq 0.05$

Table 2. Presentation of JIA in pediatric clinic during the period from 2004 to 2010.

Presentation at onset	Course of disease				Test of significance	Total (n = 63)
	Remitting (n = 30)		Unremitting (n = 33)			
	No	%	No	%		
1. Systemic onset	6	20.0	9	27.2	X^2=0.79 P=0.672	15 (23.8%)
2. Arthritis:						
A. Polyarthritis	10	33.3	12	36.4		22(35.0 %)
B. Oligoarthritis:	14	46.7	12	36.4		26 (41.2%)
	(n=14)		(n=12)		^{FE}P=0.365	
I. Oligoarthritis to polyarthritis	2	14.2	4	33.3		6(23.0%)
II. Persistent oligoarthritis	12	85.8	8	66.7		20(77.0%)
Arthralgia					X^2=3.44 P=0.064	
Yes	15	50.0	24	72.7		39(62.0%)
No	15	50.0	9	36.3		24 (38.0%)

X^2: Chi-square test $^{KW}X^2$: K*: Statistically significant at p ≤ 0.05

Table 3. Distribution of joint affection in different modes of onset of JIA in pediatric clinic during the study period.

Joints affected	SO-JIA (n=15)		Oligo-JIA (n=26)		Po-JIA (n=22)		Test of significance (P)	Total (n=63)	
	No.	%	No.	%	No.	%		No.	%
Knee	8	53.3	22	84.6	17	77.3	X^2=5.04 (0.080)	47	74.6
Ankle	12	80	17	65.4	18	81.8	X^2=2.0 (0.368)	47	74.6
Wrist	11	73.3	12	46.2	19	86.4	X^2=9.06 (0.011) *	42	66.7
Hip	7	46.6	4	15.4	9	40.9	X^2=5.61 (0.061)	20	31.7
Shoulder	0	0.0	3	11.5	0	0.0	^{MC}P=0.116	3	4.8
Elbow	7	46.6	0	0.0	12	54.5	X^2=19.38(<0.0001) *	19	30.2
Cervical spine	0	0.0	0	0.0	7	31.8	^{MC}P=0.001*	7	11.1
Sacroiliac joint	0	0.0	0	0.0	6	27.3	^{MC}P=0.002*	6	9.5
MTPs	0	0.0	0	0.0	4	18.2	^{MC}P=0.014*	4	6.3
PIPs	7	46.6	2	7.7	14	63.6	X^2=16.97 (0.0002) *	23	36.5
MCPs	0	0.0	0	0.0	13	59	^{MC}P=<0.0001*	13	20.6

Pips: Proximal interphalangeal joints MCPs: Metacarpophalangeal joints
MTPS: Metatarsophalangeal joints. X^2: Chi-square test ^{MC}P: Monte Carlo test *significant at P≤0.05

Table 4. Clinical characteristics in children according to onset of JIA

Clinical characteristics	SO-JIA (n = 15)		Oligo-JIA (n = 26)		Po-JIA (n = 22)		Test of significance	Total (n = 63)	
	No.	%	No.	%	No.	%		No.	%
Morning stiffness	10	66.7	17	65.4	15	68.2	X^2=0.04 (P=0.979)	42	66.7
Intermittent fever	12	80.0	1	3.8	3	13.6	^{MC}P<0.0001*	16	25.4
Skin rash	8	53.3	0	0.0	0	0.0	^{MC}P<0.0001*	8	12.7
Pallor	7	46.7	9	34.6	11	50.0	X^2=1.27 (P=0.530)	27	42.9
Lymphadenopathy	4	26.7	0	0.0	1	4.5	^{MC}P=0.008*	5	7.9
Hepato-splenomegaly	4	26.7	0	0.0	1	4.5	^{MC}P=0.008*	5	7.9
Uveitis	0	0.0	2	7.7	2	9.0	^{MC}P=0.670	4	6.3
Pleuritis	1	6.7	0	0.0	0	0.0	^{MC}P=0.237	1	1.6
Cardiac involvement	3	20.0	0	0.0	0	0.0	^{MC}P=0.011*	3	4.8
Renal involvement	1	6.7	0	0.0	1	4.5	^{MC}P=0.503	2	3.2
Skin involvement	3	20.0	1	3.8	1	4.5	^{MC}P=0.203	5	7.9
GIT involvement	4	26.7	1	3.8	1	4.5	^{MC}P=0.067	6	9.5
Oral diseases	1	6.7	1	3.8	1	4.5	^{MC}P=1.000	3	4.8
CNS diseases	2	13.3	0	0.0	1	4.5	^{MC}P=0.106	3	4.8

X^2: Chi-square test ^{MC}P: Monte Carlo test *significant at P≤0.05

Table 5. Laboratory parameters and results of investigations done to patients with different JIA subtypes.

Laboratory parameters	JIA sub types						Test of significance (P)	Total (n=63)	
	Po-JIA (n=22)		Oligo-JIA (n=26)		SO-JIA (n=15)				
	No.	%	No.	%	No.	%		No.	%
HB (<10 gm/dl)	11	50	9	34.6	7	46.6	X^2=1.27 (0.53)	27	42.9
WBCS (>13X10^3)	3	13.6	3	11.5	4	26.6	X^2=1.76 (0.415)	10	15.9
Platelets (<150x10^9)	6	27.2	7	26.9	8	53.3	X^2=3.54 (0.169)	21	33.3
CRP (positive results)	12	54.5	14	53.8	9	60	X^2=0.16 (0.923)	35	55.6
ESR 1st hour (>10mm/ hr.)	18	81.8	19	73	13	86.6	X^2=1.2 (0.549)	50	79.4
ESR 2nd hour (>15mm/ hr.)	20	90.9	14	53.8	11	73.3	X^2=8.06 (0.018) *	45	71.4
RF (positive results)	16	72.7	25	96.1	3	20	X^2=26.32 (0.0001) *	44	69.8
ANA (positive results)	3	13.6	10	38.5	0	0	^{MC}P=0.007*	13	20.6
Fundus examination +ve(uveitis)	2	9	2	7.7	0	0	^{MC}P=0.447	4	6.3
Chest X ray +ve findings (pneumonia±pleuritis)	3	13.6	1	3.8	2	7	^{MC}P=0.554	6	9.5

X^2: Chi-square test ^{MC}P: Monte Carlo test *significant at P≤0.05

Table 6. Relation between laboratory parameters (RF & ANA "positive cases") and the course of the disease

Laboratory Parameters	course				Test of significance (P)	Total (n=63)	
	Remitting (n=30)		Unremitting (n=33)				
	No	%	No	%		No	%
RF (positive results)	15	50.0	29	87.9	FEp = 0.003*	44	69.8%
ANA (positive results)	3	10.0	10	30.3	FEp = 0.064	13	20.6%

FEp: p value for Fisher Exact test *: Statistically significant at p ≤0.05

Table 7. Relation between the course (remitting and unremitting) of the disease and the treatment regimens.

Types of drugs used	course				Test of significance	Total (n=63)
	Remitting (n=30)		Unremitting (n=33)			
	No	%	No	%		
Single drug						
Prednisone	2	6.7	4	12.1	^{FE}P=0.674	6 (9.5%)
Methotrexate	2	6.7	6	18	^{FE}P=0.261	8(12.7%)
Naproxen	2	6.7	1	3	^{FE}P=0.601	3(4.8%)
Shifting to combined drug regimen						
Shifting to two drugs	16	53.2	9	27.3	X^2=4.46 P=0.035*	25(39.7%)
Shifting to three drugs	8	26.7	13	39.6	X^2=1.15 p=0.285	21(33.3%)

^{FE}P: Fisher's Exact test X^2: Chi-Square test

Table 8. The epidemiological data in the three Egyptian studies

Variable	Cairo study	El Sharkia	Alexandria (present study)
No of cases	196	132	63
M: F ratio	1:1.09	1:1.5	1.1:1
Age of onset (Range)	6 m-12 y	4y-15 y	3 y-14y
Age of onset (Mean)	6.25 y	10.5%	6.1y
Rural to urban	-	59.09% to 40.9%	57.1% to 42.9
Positive family history	5.6%	-	30.2%
Percent of oligoarticular	41.3%	52.2	41.2%
Percent of polyarticular	34.7%	29.2	35.0%
Percent of systemic onset	24%	13.6	23.8%
Uveitis %	5.6 %	19.6%	6.3%
Positive rheumatoid factor	-	27.2%	69.8%
Positive ANA %	18.9 %	48.5 %	20.6%
Remission rate	46.9%	-	47.4%

DISCUSSION

Worldwide, Juvenile idiopathic arthritis (JIA) has a wide range of clinical presentations and outcomes.[10] It is characterized by chronic synovitis of peripheral joints manifested as soft tissue swelling and effusion. In the current study, medical records of sixty-three children at the pediatric rheumatology clinic were retrospectively analyzed. Similar to previous studies mainly in USA, Canada, Turkey, France and Spain oligoarticular JIA was found to be the most common clinical pattern.[11,12] On contrary to Saudi Arabia study[13], systemic onset was the most common type while a Kuwaiti study conducted by Khuffash[14] in 2006 proved that there was an equal percentage between all subtypes. Moreover, our results matched previous Egyptian studies conducted in Cairo in 2009 and in El-Sharkia in 2013 but with different frequencies from ours (41.3%, 52.2%, respectively) because of variability of environmental and genetic factors.[15,16]

Most of the demographic data of the studied groups were consistent with results of previous national and international studies as the mean age of onset of the disease was (6.1±2.8 yr.), which was close to that reported in Saudi Arabia (6± 2 yr.) by Bahabri et al[12] and Mengual et al[17] in Spain (5.8±2.2 yr.). Meanwhile, age was lower than that reported by Ruperto et al[18] (8±3yr) and a cohort study at Taiwan (9.1y).[19] Also, the current study reported that most of the cases were from rural areas similar to Quartier et al[10] and Abu elsoud et al.[16] Family history of JIA showed high frequency among patients like other studies.[15, 20] On contrary, to many studies the numbers of male patients were higher than the females.[11-16] However, our results matched Ozdogan et al[21] and El-hemiari et al[22] who reported male predominance.

The Clinical profile of different subtypes of JIA was comparable to those reported in literature. knee joints were the predominately involved in oligoarticular JIA while wrist, elbow, sacroiliac joints and small joints of hand showed higher significant difference to poly articular subtype. Similar to the results reported by Viswanathakumar et al[23] (Indian study). Our results were contradictory to Bahabri et al[13] who concluded that knee joint was the least involved and this may be because the systemic onset subtype was the predominant type among Saudi children with common involvement of wrist or ankle joints.

Despite that morning stiffness was the most common presenting symptom among all subtypes, fever, skin rash, lymphadenopathy, hepatosplenomegaly and cardiac involvement showed higher significant difference to systemic onset JIA group. This was agreed by Grassi et al,[24] Chandrasekaran et al[25] and Salah et al.[15] Our study reported that pallor was the predominant extra-articular manifestations (42.2%). While Uveitis was manifested among (6.3%) of cases of oligoarticular and polyarticular subtypes. This was close to Ozdogan et al[21], El-Hemiari et al[22]and Abu Elsoud et al[16] (7%, 8.4% and 5.6%. respectively). Steinbrocker et al[26] reported that incidence of uveitis among JIA patients in Western countries was ranging between 10% and 20%. In contrast to the results of Abdwani et al[27] at 2015 (an Omani study) and Viswanathakumar et al[23] (Indian study) who reported absent cases of uveitis. The great difference observed in uveitis incidence among patients with JIA could be attributed to many factors as difficulty in diagnosis, small sample sizes leading to larger variations in reported rates and may be close relation of uveitis and positive ANA titer. Concerning ANA, it was positive among 20.6% of cases close to results of Gare et al[28] and to Salah et al[15] (18.4% and 19.9%). While others as Khuffash et al[14] and Ozdogan et al[21] reported lower results (12%, 5%) respectively. The higher percentage of positive ANA results could be attributed to higher incidence of infections inducing the illness. About 30.3% of ANA positive cases developed uveitis. Regarding other laboratory results, ESR was the most frequent raised laboratory result in all subgroups, followed by positive rheumatoid factor specially among oligoarticular subtype. Our results were nearly equal to those found in other studies.[14, 20, 27] Most of anemic patients were of polyarticular subtype near to results of Baharbi et al.[13]Meanwhile, most of CRP positive cases were of systemic onset subtype as reported by Italian study done by Melano in 2007.[29]

The management of JIA aimed to control active symptoms, achieve remission and to prevent joint damage. Since the introduction of biologic agents such as methotrexate major advances has been achieved however, non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstay of treatment. Glucocorticoids have been used usually for severe life-threatening disease, or rapidly progressive disease and uveitis. In the current study the patient outcomes and rate of remission were variable throughout the three subtypes.

The current study showed global remission rate of 47.6% among all cases. Meanwhile, the highest remission rate was observed among patients suffering from oligoarthritis followed by polyarthritis and lastly among systemic onset cases. Similar to remission rates recorded by Salah et al[15] and Khufash et al[14] (about 54%). Meanwhile, other studies reported lower rates (as 29.4%)[13,21]. This

variability in the relative frequency of the remission rate may be due to differences in environmental and genetic factors, with possible exposure to different types of infections and being subjected to different therapeutic regimens and or to the positivity of rheumatoid factor.[30]

The highest remission rate (53.2%)was found among patients who received two drugs regimen. Similar remission rate was reported by many studies[10, 14] specially Sircar et al[31] (51%) however, Weiss et al had reported higher remission rate (79%).[32]

Cases who used single drug regimen either prednisone or methotrexate and or naproxen showed lower remission rate (20.1%) in agreement to other studies.[33] No significant difference of triple therapy to double therapy on the course of the disease matched to results found by Ozdogan et al and Quartier et al.[10, 21]

Table (8) showed the epidemiological data in the three Egyptian studies - conducted in 3 governorates - including the present one.

CONCLUSION

The characteristics of JIA in Egyptian children at different areas are comparable to each other with higher frequency of oligoarticular subtype disease specially for rural areas. The discrepancies between the pattern of the disease in Egypt and those reported from Arabian Gulf countries and Western countries may be related to different immunogenic background of different ethnic groups, a point that needs further studies.

Future studies are necessary to clarify the role of other therapeutic alternatives in treatment and to elucidate the implications of different therapeutic regimens on long term morbidity and mortality.

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REFERENCES

1. **Cassidy JT, Pretty RE, Laxer RM, Linsley CB**, editors. Textbook of pediatric rheumatology. 5th ed. Philadelphia: Elsevier Saunders; 2005; 206-260.
2. **Ravelli A, Martini A.** Juvenile idiopathic arthritis. The Lancet 2007; 369: 767-779.
3. **Michael LM, James TC.** Juvenile Idiopathic Arthritis. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, eds. Nelson Textbook of Pediatrics. 19th ed, Philadelphia: Saunders Elsevier 2011: 799-805.
4. **Masters SL, Simon A, Aksentijevich I, Kastener DL.** The molecular pathophysiology of autoinflammatory disease. Annu Rev Immunol 2009; 27: 621–668.
5. **Prahalad S.** Genetics of juvenile idiopathic arthritis: an update. Curr Rheumatol 2004; 16: 588–594.
6. **Petty RE, Southwood TR, Manners P, et al.** International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis: Second Revision, Edmonton 2001. J Rheum 2004; 31: 390–4.
7. **Johnson K, Gardner-Medwin J.** Childhood arthritis: classification and radiology. Clin Radiol 2002; 57: 47–58.
8. **Milojevic DS, Ilowite NT.** Treatment of rheumatic diseases in children, special considerations. Rheum Dis Clin North Am 2002; 28: 461–482.
9. **Mc Cann L, Wedderburn L, Hassan N.** Juvenile idiopathic arthritis. Arch Dis Child Educ Pract Ed 2006; 91: 29–36.
10. **Quartier P, Prieur AM.** Juvenile idiopathic arthritis. Clinical aspects. Clin Exp Rheumatol 2007; 57: 1171-1178.
11. **Demirkaya E, Özen S, Bilginer Y, Ayaz NA, Makay BB, Unsal E, et al.** The distribution of juvenile idiopathic arthritis in the eastern Mediterranean: results from the registry of the Turkish pediatric rheumatology association. Clinical and Experimental Rheumatology 2011:29; 111–116.
12. **C. Modesto, J. Antón, B. Rodriguez, Bou R, Arnal C, Ros J, et al.** Incidence and prevalence of juvenile idiopathic arthritis in Catalonia (Spain). Scandinavian Journal of Rheumatology 2010: 39; 472–479.
13. **Bahabri S, Al-Sewairi W, Al-Mazyad A, Karrar A, Al-Ballaa S, El-Ramahai K, et al.** Juvenile rheumatoid arthritis: The Saudi experience. Ann Saudi Med 2001; 4:413-418.
14. **Khuffash FA, Majeed HA.** Juvenile rheumatoid arthritis among Arab children. Scand J Rheumatol 2006; 17: 393-395.
15. **Salah S, Hamshary A, Lotfy H, Abdel Rahman H.** Juvenile Idiopathic Arthritis, the Egyptian Experience. Journal of Medical Sciences 2009;9: 98-102.
16. **Abou El-Soud A, El-Najjar A, El-Shahawy E, Amar H, Hassan T, Abd-Allaha S, Ragab H.** Prevalence of juvenile idiopathic arthritis in Sharkia Governorate, Egypt: epidemiological study. Rheumatol Int 2013; 33:2315–2322

17. **Mengul M, Fernandez JM, Sanchez GS, Diaz MF, Gonzalez NF, Guerrero SM.** Epidemiological study of juvenile arthritis in the last sixteen years in Spain. Anal Pediatr 2007; 66: 24-30.
18. **Ruperto N, Murray KJ, Gerloni V, Wulffort N, de Oliveira SK, Falcini F, et al.** A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. Arthritis Rheum 2004; 50: 2191–2201.
19. **Shen CC, Yeh KW, Ou LS, Yao TC, Chen LC, Huang JL.** Clinical features of children with juvenile idiopathic arthritis using the ILAR classification criteria: a community-based cohort study in Taiwan. Journal of Microbiology, Immunology and Infection 2013; 46: 288–294.
20. **Zeft A, Shear ES, Thompson SD, Glass DN, Prahalad S.** Familial autoimmunity: maternal parent-of-origin effect in juvenile idiopathic arthritis. Clin Rheumatol. 2008 27 :241-244.
21. **Ozdogan H, Kasapopur O, Dede H, Arisoy N, Bicerene T, Yurdakul S, et al.** Juvenile chronic arthritis in a Turkish population. Clin Exp Rheumatol 1991; 9: 431-435.
22. **Al-Hemairi M, Albokhari S, Muzaffer M.** The Pattern of Juvenile Idiopathic Arthritis in a Single Tertiary Center in Saudi Arabia. International Journal of Inflammation 2016.
23. **Viswanathakumar HM, Kumar G.** Study of clinical spectrum of juvenile idiopathic arthritis in children in a tertiary referral hospital. Curr Pediatr Res 2014; 18 :21-25.
24. **Grassi W, De Angelis R, Lamanna G.** The clinical features of rheumatoid arthritis. Eur J Radiol 2003; 27: 18-24.
25. **Chandrasekaran AN, Rajendran CP, Madhavan R.** Juvenile rheumatoid arthritis-Madras experience. Indian J Pediatr 2005; 4: 501-510.
26. **Steinbrocker O, Traeger CH, Batterman RC.** Therapeutic criteria in rheumatoid arthritis. J Am Med Assoc 2001; 140: 659-662.
27. **Abdwani R, Abdalla E, Al Abrawi S, Al-Zakwani I.** Epidemiology of juvenile idiopathic arthritis in Oman. Pediatric Rheumatology 2015; 13:3
28. **Gare B, Fasth A.** The natural history of juvenile chronic arthritis: A population-based cohort study. Onset and disease process. J Rheumatol 2004; 22: 295-306
29. **Melano H, Roperto J, Tanini O.** The clinical features of rheumatoid arthritis. Eur J Radiol 2007; 34; 456-464
30. **Chantler JK, Tingle AJ, Petty RE.** Persistent rubella virus infection associated with chronic arthritis in children. N Engl J Med 2005; 313: 1117-1123.
31. **Sircar D, Ghosh B, Ghosh A, Hidar S.** Juvenile idiopathic arthritis. Indian Pediatr 2006; 43:429-433.
32. **Weiss JE, Ilowite NT.** Juvenile idiopathic arthritis. Pediatr Clin. North Am J 2005; 52: 413-442.
33. **Borchers A, Selim C, Cheema G, Keen CL, Shoenfeld Y, Gershwin ME, et al.** Juvenile idiopathic arthritis. Autoimmune Rev 2006; 5: 279-298.