The Epidemiological Profile of Juvenile Idiopathic Arthritis: Single Center Study in Delta Region of Egypt

Ahmed M El-Refaey (arefaey72@mans.edu.eg)
Mansoura University
Neven Nashat Sobh
Mansoura University
Dina Shahin
Mansoura University
Ahmad Darwish
Mansoura University

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Abstract

Background

Juvenile idiopathic arthritis (JIA) is children's most common autoimmune musculoskeletal disease. The spectrum of patients' profiles of JIA showed many similarities and differences among different populations.

Aim of the work

The purpose of this study is to determine the prevalence, subtypes, distribution, and characteristic features of JIA among children in Rheumatology outpatient clinic at Mansoura University Children's Hospital (MUCH).

Patients and methods

The study was a cross-sectional observational study carried out in the rheumatology outpatient clinic in Mansoura University children's Hospital, on 73 patients diagnosed with JIA according to the International League of Associations for Rheumatology (ILAR) from April 2019 to April 2020.

Results

There was a statistically significant difference between JIA types as regard age of patients, age of onset of disease, duration of the disease affected at the time of diagnosis, fever, rash, and organomegaly with the highest value in psoriatic type. There was a statistically significant difference in methotrexate (MTX), Humera, Enbrel, and Leflunomaide usage between JIA subtypes. The severity of the disease was correlated significantly with laboratory parameters including the erythrocyte sedimentation rate, C reactive protein, and platelets count. MTX, Pulse steroid, Actemra, and Lefluonamide usage differed significantly according to the severity of the disease while Humera, Endoxan, Enbrel, and NSIAD showed no significant difference.

Conclusion

The types of JIA differ significantly from each other as regards fever, rash, and organomegaly with an increase in systemic onset rather than other types. While ophthalmic affection shows no significant difference between JIA subtypes. A low percentage of cases had uveitis indicating low severity of disease in the studied cases. Biological treatment was given to severe and resistant cases when indicated.

Introduction

One of the most is the most common cause of arthritis in childhood is Juvenile Idiopathic Arthritis (JIA). Its incidence is about 300,000 children in North America. JIA has several subtypes of chronic arthritis that have varying clinical features. Each of these subtypes has a different prognosis, complications, and

treatment. The precise etiology of JIA is unknown and is likely the result of a complex interaction between genetic factors and environmental factors. (1).

The prevalence and incidence of JIA have been found to differ in different ethnic groups and regions (2). The lowest prevalence (3.43 per 100,000) was reported in Egypt and the highest (196 per 100,000) was reported in South America (3). In the unites states, the prevalence of JIA from different published studies has ranged from 1.6 to 86.1 per 100,000 (4).

Juvenile idiopathic arthritis is a clinical diagnosis in most conditions. There are no specific diagnostic tests. An elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) indicate an inflammation process. Importantly, part of the workup is designed to rule out other childhood causes of arthritis. Synovial fluid analysis may be used to rule out many conditions, such as Lyme arthritis and septic arthritis (1).

Laboratory workup may reveal anemia, thrombocytopenia, leukocytosis or leukopenia, an elevated LDH and uric acid, and blasts on the peripheral smear (5). A positive ANA is a risk factor for the development of uveitis (6). Frequent ophthalmologic screening is needed to detect asymptomatic uveitis (7).

The incidence, prevalence, and clinical presentations vary among the ethnic and geographically different populations. Few Egyptian studies described the clinical profile of affected children which was our motivation to conduct this study to determine the prevalence, subtypes, distribution, and characteristic features of JIA among children in the Rheumatology outpatient clinic at Mansoura University Children's Hospital.

Patients And Methods

The study was a cross-sectional observational study carried outon 73 patients diagnosed with JIA according to the International League of Associations for Rheumatology (ILAR) from April 2019 to April 2020.

The medical records of the pediatric patients were reviewed, and information collected including the age of patients, gender, age at diagnosis, the pattern of disease onset, disease duration, JIA subtypes, presence of fever, rash, organomegaly, and eye screening for diagnosis of uveitis and conjunctivitis.

Laboratory investigations included white blood cells (WBCs) count, Hematocrit level, platelets (PLT) count, hemoglobin level (Hb), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), SGOT, SGPT and Immunological parameters (ANA, RF, HLA-B27).

Also, the study assessed different therapeutic protocols including retrospective history for the detailed treatment the patient received before the study.

The study included an assessment of the disease activity using the JADAS-27 score and Juvenile Spondyloarthritis Disease Activity Score.

The study was approved by the institutional review board (IRB) of Mansoura University, and informed consent was obtained from the children's parents. All methods used in this study were performed in accordance with the IRB guidelines and regulations.

Statistical Analysis And Data Interpretation

Qualitative data were described using numbers and percentages. Quantitative data were described using median (minimum and maximum) for non-parametric data and mean, and standard deviation for parametric data after testing normality using the Kolmogorov-Smirnov test. The significance of the obtained results was judged at the (0.05) level. Data were fed to the computer and analyzed using IBM SPSS Corp. Released in 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp

Results

Age of patients, age of onset of disease, duration of the disease, and gender showed a significant difference between types of JIA while residence shows no significant difference between JIA subtypes **(Table 1).**

There was a statistically significant difference between JIA types as regard fever, rash, and organomegaly with an increase in systemic onset rather than other types. While ophthalmic affection showed no significant difference between JIA subtypes **(Table 2).**

There was a statistically significant difference between joint affected at the time of diagnosis and subtypes of JIA **(Table 3).**

There was a statistically significant difference between WBCs, PLT, SGOT, SGPT, CRP, and ESR among JIA subtypes with the highest value in systemic onset. On the other side, Hb was the lowest value in systemic onset. HLAB27, ANA, RF, and CR showed no significant difference **(Table 4).**

There was no significant difference in disease severity among JIA subtypes **(Table 5).** There was a statistically significant difference in methotrexate (MTX), Humera, Enbrel, and Leflunomaide usage between JIA subtypes. While Duration of therapy, non-steroidal anti-inflammatory drugs (NSAIDs), Endoxan, Actemra, and pulse steroid usage showed no significant difference between JIA subtypes **(Table 6).**

Age/years, Age of onset/years, Duration of disease/years, Gender, and Residence had no significant effect on the severity of JIA **(Table 7).** PLT, CRP, and ESR correlated significantly with the severity of the disease while other laboratory parameters had no significant effect **(Table 8).** MTX, Pulse steroid, Actemra, and Lefluonamide usage differed significantly according to the severity of the disease while Humera, Endoxan, Enbrel, and NSIAD showed no significant difference **(Table 9).**

Table (1): Comparison between types of JIA as regards sociodemographic characteristics of the studied cases.

	Types of JIA					test of significance
	Polyarticular (32)	Systemic onset (20)	Oligoarticular (10)	ERA (9)	Psoriatic (2)	
Age/years	13.19 ± 3.42	7.68 ± 3.46	9.75 ± 3.76	10.28 ± 3.62	16.50 ± 2.12	F = 9.35 P < 0.001*
Age of onset/years	9.92 ± 4.01 10(3–17)	5.78 ± 2.85 5.5 (2.5–15)	6.90 ± 2.51 7(3.5–11)	7.61 ± 1.62 8(4–9)	11.0 ± 7.07 11(6–16)	F = 5.39 P = 0.001*
Duration of disease/years	2.0 (0.5-9.0)	1.5 (0–5)	3.75 (0.5-4.0)	1.5 (0.5-8.0)	5.5 (2–9)	KW p < 0.001*
Gender Male Female	22(68.8%) 10(31.2%)	9(45.0%) 11(55.0%)	2(20.0%) 8(80.0%)	4(44.4%) 5(55.6%)	2(100%) 0(0.0%)	MC P = 0.039*
Residence Urban Rural	13(40.6%) 19(59.4%)	6(30%) 14(70%)	4(40%) 6(60%)	4(44.4%) 5(55.6%)	0 2(100%)	MC P = 0.731

F: One Way ANOVA test, MC: Monte Carlo test, KW: Kruskal Wallis test *statistically significant if p<0.05 parameters described as mean± SD, median (8), number (percentage)

Table (2): **Comparison between types of JIA as regards clinical presentation of the studied cases.**

	Types of JIA					Test of significance
	Polyarticular	**Systemic onset**	**Oligoarticular**	**ERA**	**Psoriatic**	
Fever	**5** (15.6%)	**20** (100%)	**1** (10.0%)	**1**(11.1%)	**0**	MC P < 0.001*
Rash	**3** (9.4%)	**15** (75%)	**0**	**0**	**1** (50%)	MC P < 0.001*
Organomegaly	**2** (6.2%)	**6** (30.0%)	**0**	**0**	**0**	MC P = 0.03*
Ophthalmic	**23** (71.9%)	**17** (85%)	**7** (70%)	**6** (66.7%)	**1**(50%)	MC
Free	**5** (15.6%)	**2** (10%)	**1** (10%)		**1**(50%)	P = 0.730
Conjunctivitis	**4** (12.5%)	**1** (5.0%)	**2** (20%)	**1** (11.1%)	**0**	
Anterior uveitis				**2** (22.2%)		

MC: Monte Carlo test *statistically significant if p < 0.05 parameters described as number (percentage)

Table (3): **Comparison between types of JIA as regards joint affected at the time of diagnosis.**

	Types of JIA					Test of significance
First affected joint	**Polyarticular**	**Systemic onset**	**Oligoarticular**	**ERA**	**Psoriatic**	
Wrist	**8 (25%)**	**8 (40%)**	**1 (10%)**	**1(11.1%)**	**0**	**MC**
Shoulder	**1 (3.1%)**	**0**	**0**	**0**	**0**	**P = 0.031***
Sacroiliac joint	**0**	**0**	**0**	**3(33.3%)**	**0**	
Knee	**7 (21.9%)**	**8 (40%)**	**6 (60%)**	**2(22.2%)**	**1(50%)**	
Hip	**1(3.1%)**	**1 (5%)**	**0**	**0**	**0**	
Hand	**7 (21.9%)**	**1 (5%)**	**0**	**0**	**1 (50%)**	
Foot	**1(3.1%)**	**0**	**0**	**0**	**0**	
Elbow	**3 (9.4%)**	**0**	**0**	**0**	**0**	
Ankle	**4 (12.5%)**	**2 (10%)**	**3 (30%)**	**3 (33.3%)**	**0**	

MC: Monte Carlo test *statistically significant if p < 0.05. parameters described as number (percentage)

Table (4) comparison between types of JIA as regards serological and biochemical features among studied cases.

	Types of JIA					Test of significance
	Polyarticular	Systemic onset	Oligoarticular	ERA	Psoriatic	
HLAB27	0	0	1 (50%)	2 (100%)	1 (25%)	MC P = 0.268
ANA	12 (37.5%)	2 (10%)	3 (30%)	2 (22.2%)	0	MC P = 0.222
RF	11 (34.4%)	3 (15%)	0	1 (11.1%)	1 (50%)	MC P = 0.09
WBCS	7.8 (3–51)	15.5 (9–29)	5.65 (4–11)	8.4 (4.5–12)	7 (5–9)	KW P < 0.001*
HB	10.89 ± 1.63	9.31 ± 1.23	10.03 ± 1.59	10.59 ± 2.01	13.50 ± 0.71	F = 5.32 P = 0.001*
PLT	302 (42.0-691)	454.5 (340–750)	357 (188–705)	362 (240–536)	330 (260–400)	KW P < 0.001*
SGOT	24 (0.4–54)	47.5 (19–230)	27 (20–45)	25 (13–31)	24.5 (21–28)	KW P < 0.001*
SGPT	20 (13–114)	66 (18–516)	28 (15–48)	23 (16–45)	17.5 (15–20)	KW P < 0.001*
CR	0.564 ± 0.131	0.630 ± 0.138	0.590 ± 0.074	0.644 ± 0.13	0.550 ± 0.07	F = 1.28 P = 0.285
CRP	6 (0-180)	77.5 (0-360)	0 (0-108)	18 (0–82)	29.5 (24–35)	KW P = 0.015*
ESR1	34.5 (5-135)	88 (20–130)	27.5 (18–97)	2 (12–62)	46 (20–72)	KW P = 0.012*

F: One Way ANOVA test, MC: Monte Carlo test, KW: Kruskal Wallis test *statistically significant if p < 0.05 parameters described as mean ± SD, median (8), number (percentage)

Table (5): Disease severity between different groups of JIA.

	Types of JIA					Test of significance
Severity	Polyarticular	Systemic onset	Oligoarticular	ERA	Psoriatic	
Mild	18 (56.2%)	6 (30%)	8 (80%)	5 (55.6%)	1 (50%)	MC P = 0.415
Moderate	12 (37.5%)	11 (55%)	2 (20%)	3 (33.3%)	1 (50%)	
Severe	2 (6.2%)	3 (15%)	0	1 (11.1%)	0	

MC: Monte Carlo test, *statistically significant if $p < 0.05$ parameters described as number (percentage)

Table (6): **Frequency of drug usage among different types of JIA.**

	Types of JIA					Test of significance
	Polyarticular	Systemic onset	Oligoarticular	ERA	Psoriatic	
Duration of therapy/ years	1.75 (0.2-9)	1 (0.05-5)	3 (0.6-4.0)	2 (0.5-5)	5 (1–9)	KW P = 0.755
NSIAD	13 (40.6%)	6 (30%)	5 (50%)	7 (77.8%)	0	MC P = 0.107
MTX	28 (87.5%)	18 (90%)	10 (100%)	3 (33.3%)	2 (100%)	MC P = 0.001*
Pulse steroid	4 (12.5%)	5 (25%)	2 (20%)	1 (11.1%)	1 (50%)	MC P = 0.550
Actemra	2 (6.2%)	5 (25%)	1 (10%)	1 (11.1%)	0	MC P = 0.354
Humera	0	0	0	3 (33.3%)	0	MC P < 0.001*
Endoxan	0	1 (5%)	0	0	0	MC P = 0.612
Enbrel	0	0	0	2 (22.2%)	0	MC P = 0.006*
Lefluonamide	0	5 (25%)	0	0	0	MC P = 0.007*
KW: Kruskal Wallis test *statistically significant if p < 0.05 parameters described as median (8) ,						

Table (7): **Comparison between grades of JIA as regard sociodemographic characteristics of the studied cases.**

	Severity of JIA			test of significance
	Mild	Moderate	Severe	
Age/years	11.38 ± 4.58	10.52 ± 3.76	10.17 ± 4.31	F = 0.448 P = 0.641
Age of onset / years	**9.0** (2.5–17)	**6.5** (3–15)	**7.5** (3–13)	KW P = 0.124
Duration of disease/years	**2.0** (0.5-8)	**3.0** (0.5-9)	**2** (0–4)	KW P = 0.110
Gender **Male** **Female**	**21** (55.3%) **17** (44.7%)	**15** (51.7%) **14** (48.3%)	**3** (50%) **3** (50%)	MC P = 0.945
Residence **Urban** **Rural**	**16** (42.1%) **22** (57.9%)	**8** (27.6%) **21** (72.4%)	**3** (50%) **3** (50%)	MC P = 0.375

F: One Way ANOVA test, MC: Monte Carlo test, KW: Kruskal Wallis test *statistically significant if p < 0.05 parameters described as mean ± SD, median (8), number (percentage)

Table (8): **Comparison between grades of JIA as regards** laboratory findings of the studied cases.

	Severity of JIA			
	Mild	Moderate	Severe	test of significance
HLAB27	**2** (40%)	**1** (50%)	**1** (50%)	MC P = 0.956
ANA	**9** (23.7%)	**7** (24.1%)	**3** (50%)	MC P = 0.377
RF	**9** (23.7%)	**6** (20.7%)	**1** (16.7%)	MC P = 0.909
WBCS	**9.0** (3.3–51)	**10** (3.0–29)	**13.5** (4.7–29)	KW P = 0.09
HB	10.79 ± 1.68	9.94 ± 1.72	9.75 ± 1.87	F = 2.48 P = 0.09
PLT	**300** (188–750)	**416** (42–723)	**382.5** (260–644)	KW P = 0.034*
SGOT	**25.5** (10–82)	**30** (0.4–200)	**35** (17–230)	KW P = 0.342
SGPT	**25** (13–114)	**38** (15–516)	**36** (17–118)	KW P = 0.271
CR	0.595 ± 0.117	0.584 ± 0.135	0.643 ± 0.16	F = 0.531 P = 0.591
CRP	**0** (0-136)	**62** (0-360)	**111** (0-180)	KW P = 0.001*
ESR1	**25** (5–97)	**72** (30–130)	**118.5** (55–135)	KW P = 0.001*

F: One Way ANOVA test, MC: Monte Carlo test, KW: Kruskal Wallis test *statistically significant if p < 0.05 parameters described as mean ± SD, median (8), number (percentage)

Table (9): Comparison between grades of JIA as regard type of drugs used among studied cases.

	Severity of JIA			
	Mild	Moderate	Severe	test of significance
Duration of therapy / years	**1** (0.2-6)	**2** (0.5-9)	**2** (0.05-4)	KW P = 0.288
NSIAD	**18** (47.4%)	**10** (34.5%)	**3** (50%)	MC P = 0.530
MTX	**27** (71.1%)	**29** (100%)	**5** (83.3%)	MC P = 0.007*
Pulse steroid	**0**	**9** (31%)	**4** (66.7%)	MC P < 0.001*
Actemra	**0**	**4** (13.8%)	**5** (83.3%)	MC P < 0.001*
Humera	**0**	**2** (6.9%)	**1** (16.7%)	MC P = 0.10
Endoxan	**0**	**1** (3.4%)	**0**	MC P = 0.463
Enbrel	**1** (2.6%)	**1** (3.4%)	**0**	MC P = 0.893
Lefluonamide	**0**	**2** (6.9%)	**3** (50%)	MC P < 0.001*

MC: Monte Carlo test KW: Kruskal Wallis test *statistically significant if p < 0.05 parameters described as median (8), number (percentage).

Discussion

Juvenile idiopathic arthritis is the most common chronic pediatric rheumatic disease and an important cause of acquired impairment and disability in children and adolescents. It is presented in different clinical presentations (e.g., oligoarthritis, polyarthritis, and, systemic arthritis) (1). There is no specific laboratory test for diagnosis of the disease despite the well-defined clinical manifestations. In the absence of definitive diagnostic criteria, many classifications and diagnostic criteria have been used depending mainly on the number of joints involved, disease activity, positive rheumatoid factor (RF), and associated clinical signs (9).

The therapeutic protocols for the management of JIA are variable, starting with NSAIDs, systemic or intra-articular corticosteroids, traditional disease-modifying antirheumatic drugs (DMARDs), and updated novel biologic agents. The treatment recommendations and standards of care for JIA have been published (10).

This study aimed to determine the prevalence, subtypes, distribution, and characteristic features of JIA among children in the Rheumatology outpatient clinic at Mansoura University Children's Hospital (MUCH). In the present study, we found that the prevalence of JIA was 30%. Abou El-Soud et al 2013 (11) conducted a study in Sharkia Governorate (Egypt) and found that the point prevalence of JIA was 3.43 per 100,000. The prevalence of JIA in boys was 2.58 per 100,000 and in girls was 4.33 per 100,000. Abdwani et al 2015 (12) found that the incidence in Oman was 2/100,000 with a prevalence of JIA of 20/100,000. Differences in the prevalence rate reported in our study may be explained by knowing that our study represented the prevalence of JIA in a single center while other studies estimated community-based prevalence and incidence.

Though it is well recognized that among JIA cases females always outnumber males (13), the present study was conducted on 73 subjects most patients were males 39 (53.4%) and 34 were females (46.6%). This finding might be explained by our socio-cultural background, where male children are given more care and are brought to the hospitals more frequently than female children. Also, genetic, and environmental factors, as well as infectious agents, are risk factors for developing JIA. Certain types of JIA such as enthesitis-related JIA where patients often have the HLA-B27 haplotype typically affect boys more commonly than girls. The estimated ratio of boys to girls in enthesitis-related JIA is 1.5 : 1(14).

Our results were comparable to Weakley et al. 2012 (15) as they found that there was an exactly equal female-to-male ratio: 39 males and 39 females. On the other hand, San Ildefonso and Pascual 2014 (16) found female predominance in their study (61.4%) versus 38.6%) boys.

In the present study, the mean age was 10.94 ± 4.22 ranging from 3 to 18 years which was similar to Savioli et al., 2004 (17) who found that the mean age of the patients with juvenile idiopathic arthritis was 10.8 years. On the other side, this finding was higher than other studies. Al-Hemairi et al., 2016 (18) who found that the mean age of onset of JIA symptoms in their patients was 7.11 ± 3.65 years (range: 8 months–14.5 years). Also, Alsulami et al., 2017 (19) found that the average age at diagnosis of the population was 7.44 ± 4.52 years. Furthermore, the mean age of onset of disease/years was 8.12 ± 3.78 ranging from 2.5 to 17 years which was higher than del Val et al 2019 (20) who found that the median age at onset was 5 years (IQR, 2.4–11.8) and the median age at diagnosis was 5.1 years (IQR, 2.6–12.1). One of the reasons for these results could be that the present studies' patients are being referred to treatment centers relatively long after their initial onset of symptoms due to low socioeconomic state, abundant parenteral negligence and ignorance, non-educated families, and ineffective primary health care system and therefore an older group of children actively attend our clinics.

Most of our patients were from rural areas (63%). The mean duration of disease/years was 2.82 ± 2.2 which was nearly similar to Elsayed Mostafa et al., 2019 [21] study conducted in Zagazig, Egypt as the majority were living in rural areas (67%) with a low socioeconomic status (67%). This may be explained by an association between exposure to enteric bacteria (gut pathogens and pathobionts and enthesitis-related arthritis in rural areas where gastrointestinal infections are more common (22). Also, Zeft et al., 2014 (23) analyzed the association between short-term air conditions and JIA onset, elevated PM2.5 concentrations were associated with an increased risk of JIA onset in children younger than 5.5 years, with stronger effects seen in boys and children with systemic JIA.

In our study, we found that age, age of onset of disease, duration of the disease, and gender showed a significant difference between types of JIA while residence showed no significant difference between JIA subtypes. Our result was in line with previous studies by Abdwani et al 2015 (12) who found a difference in age and sex between oligoarticular, polyarticular and systemic onset JIA. Also, Packham and Hall 2002 (24) found that the age at disease onset was significantly lower in the oligoarticular, extended oligoarticular and polyarticular (rheumatoid factor-negative) JIA subsets and significantly higher in the polyarticular (rheumatoid factor-positive), enthesopathy-related and psoriatic JIA subsets.

Our study showed that the weight mean was 23.42 ± 18.29 ranging from 5th to 75th percentile. The height means was16.37 ± 12.81 ranging from 5th to 50th percentile. Weight and height showed no significant difference between JIA types. Similarly, Alsulami et al 2017 (19) found no difference between different JIA sub-types in any of the growth parameters.

In the present study, fever occurs in 37% of cases, rash in 26.3%, and organomegaly in 11% of cases. Sayed et al 2019 (25) found that all studied cases presented with arthritis at the time of diagnosis. Overall, 50% of the studied cases presented with fever, 30% of the studied cases presented with skin rashes and lymphadenopathy, and 20% of the studied cases presented with organomegaly.

Furthermore, our study showed that most patients were free from ophthalmic affection (74%), 13.7% of patients were suffering from conjunctivitis while 12.3% of patients have anterior uveitis which was nearly similar to the percentage reported by Ben Ezra et al., 2007 (26) in which 11.6% of patients with JIA enrolled in their study had uveitis, but higher than Berthold et al., 2019 (27) who found that uveitis occurred in 10.8% of the children. While, Nordal et al., 2017 (28) reported higher rates in Denmark, Finland, Sweden, and Norway (20.5%).

The difference observed in uveitis incidence among patients with JIA could be attributed to many factors such as difficulty in diagnosis, small sample sizes leading to larger variations in reported rates, and maybe close relation between uveitis and positive ANA titer. Also, the predictors of uveitis are different in girls and boys, even though the rate of uveitis did not differ. This may reflect that different categories of JIA have different types of uveitis with different predicting factors (29).

In the present study, we found a statistically significant difference between JIA subtypes as regard fever, rash, and organomegaly with an increase in systemic onset rather than other types. However, ophthalmic

affection showed no significant difference between JIA subtypes.

In agreement with our results Hegde et al., 2020 (30) found that fever, rash, lymphadenopathy, and hepatosplenomegaly were exclusively seen in SOJIA. None of the other JIA subtypes showed any extra-articular manifestations.

In our study, the most frequently affected joint was the knee joint (32.9%), followed by the wrist joint (24.7%), ankle (16.4), hand (12.3%), elbow and sacroiliac joint (4.1%), hip joint (2.7%), shoulder and foot (1.4%). Nandi et al., 2009 (31) and Tanya et al., 2020 (32) found a statistically significant difference between joint affected at the time of diagnosis among subtypes of JIA. This was in the same line with previous studies which reported that the knee joint was the most frequently affected. Also, Marzetti et al 2017 (33) found that the most commonly affected joints were the knee (74.1%) followed by the small joints of hands and feet (27.1%), and the wrist (19.2%); hip (15.2%) and elbow joints (10.6%) were affected less frequently.

In the present study, ANA was positive in 26% of cases which is similar to a previous study by Lotfy et al 2009 (34) as ANA was positive in 26% of cases. Moreover, RF was positive in 21.9% of cases which was higher that Shen et al 2013 (35) who found that a total of 10 children (5.1%) were positive for RF, of whom nine had seropositive polyarthritis and one had undifferentiated arthritis. Positivity of HLA-B27 and ANA titer were found in (32.3%) and (33.3%) cases, respectively. Also, we found that HLAB27 in 5.5% of cases which was lower than Berthold et al., 2019 (27) who found that 14.7% are carriers of HLAB27; 48.6% of them have ER.

In the present study, most patients had mild disease activity (52.1%). Bulatovic et al 2014 (36) opposed our results as they found that (30.5%) of patients had low disease activity with a median JADAS-27 of 0.5 (IQR 0.02.7), whereas (18.4%) of patients had high disease activity. Also, Abdwani et al.,2015 (12) found that disease activity grade (JADAS-27) in JIA patients group, there were (60%) of patients with moderate disease activity and (40%) of patients with high disease activity. Our study showed no significant difference in disease severity between JIA subtypes. In agreement with our results, Huang et al 2021 (37) studied thirty-five non-systemic JIA patients with a total of 62 visits. JIA disease activity was shown as the physician's global assessment of disease activity (PGA) score. The PGA score among the JIA subtypes showed no significant difference. The physician's global assessment of disease activity was rated according to chief complaints, symptoms, signs, and the findings of physical examinations. The PGA was given as a numerical score on a visual analog scale (VAS) of 0–100 mm (where 0 = no disease activity and 100 = maximum disease activity).

Another study by Albers et al 2010 (38) observed differences in the percentages of active disease between JIA subtypes. This may be explained by using a sum of parameters of the involved joints which may underestimate the disease severity in the subtypes with less affected joints.

In the present study, the most common DMARDs used were MTX (83.6%), followed by Steroids (52.1%), NSAID in 42.5%, and pulse steroids in 17.8%. Endoxan and Lefluonamide were the least drugs used 1.4%

and 6.8% respectively. In agreement with our results Patra and Kumar, 2018 (39) conducted a retrospective hospital-based study in the pediatric rheumatology clinic of the All India Institute of Medical Sciences, steroid was used in 56% of cases. Among DMARDs, methotrexate was the most commonly used drug. The combination of DMARDs was used in five children. Contrarily, Beukelman et al., 2017 (40) found that participants received methotrexate or a biological agent following their enrollment. Also, Alzyoud et al., 2021 (41) found that NSAIDs were used in (82.8%) of patients. Steroids were administered to the majority of the patients (91%) patients. Disease-modifying anti-rheumatic drugs were used in (94.2%) of patients, and methotrexate was the most common DMARD used (81.4%) in patients). In the present study, the biological therapy used was Actemra in 12.3%, Humera in (4.1%), and Enbrel in (2.7%) which was more than a study conducted in India by Patra and Kumar, 2018 who evaluated that biologics could not be used in any case due to financial constraints but lower than Rocha et al., 2019 (42) who found that Biologic DMARD (bDMARD) was being used by 46 (28%) of the patients And Alzyoud et al., 2021[(41)] who found that biological treatment was used in half of the patients (50%). Similar to our results Alqahtani 2020 (43) showed that adalimumab is the most common biological treatment.

In our study, Actemera has used in 9 cases 2 of them had severe disease activity, 2 had persistent elevated inflammatory markers, 2 had persistent systemic manifestations, 1 had moderate disease activity, 1 had persistent arthritis, and 1 had a failure of conventional therapy. De Benedetti et al 2012 found that Actemra was given to four cases that were resistant to all given treatment. Bielak et al 2018 (44) performed a study in Germany that showed a favorable outcome under tocilizumab treatment reported for (69.6%) of the patients.

A study in Spain by Calvo et al 2017[(45)] found TCZ may be an effective therapy for severe JIA-associated uveitis refractory to conventional immunosuppressive and biological drugs including anti-TNF and other biologic agents such as RTX or ABA. Tappeiner et al 2018 (46) observed that TCZ treatment achieved suppression of uveitis in 2 of 3 patients in whom disease had been refractory to the previous DMARD, including at least 1 TNF-α inhibitor. Our study showed that Humera was used in 3 cases 1 had acute anterior uveitis and 2 patients had persistent disease activity. Also, Horton et al 2019 (47) Adalimumab was well tolerated and visual acuity outcomes were excellent.

Furthermore, Horneff et al 2018 (48) found that ADA is well tolerated in patients with active poly-articular course JIA during long-term exposure, Overall, the 7-year safety data from this registry support the known safety profile of ADA.

The difference in treatment between our study and previous studies with decreased biological treatment in our study may be explained by the high cost of these drugs which can’t be afforded by our patients.

In the present study, Endoxan was used in 1 patient who had CNS vasculitis. Enbrel was used in 2 patients; 1 had persistent disease activity and the other was used as an alternative to MTX. Lefluonamide was used in 5 cases; 2 had persistent systemic manifestation in 2 patients in combination with MTX in low doses and in one with MAS.

In the present study, we found a statistically significant difference between MTX, Humera, Enbrel and Lefluonamide usage in JIA subtypes. While Duration of therapy, NSIAD, Endoxan, Actemra, and pulse steroid usage showed no significant difference between JIA subtypes

Also, we found a statistically significant difference in WBCs, PLT, SGOT, SGPT, CRP, and ESR between subtypes of JIA with the highest value in systemic onset while Hb was the lowest value in systemic onset. However, HLA-B27, ANA, RF, and serum creatinine showed no significant difference. Sen et al 2015 (49) agreed with our results as they found that the frequency of anemia was changed from 31.6–49.3% in subgroups with the most frequent in the polyarthritis group. Hegde et al 2020 (30) found that the acute phase reactants like ESR, CRP, and serum ferritin were higher in SOJIA than any other subtypes. other studies opposed our results Hussein et al., 2018 (50) and Şen et al., 201*5* (19) as they found no significant differences between subgroups as regards CRP, ESR, and anemia.

In our study, Age/years, Age of onset / years, Duration of disease/years, Gender, and Residence had no significant effects on the severity of JIA.

In agreement with our results, Albers et al 2010 (38) observed no differences in age at onset, sex, and ANA status between patients with a remitting course and those with an unremitting course.

Contrary to our results Chia et al 2003 (51) noted that the proportion of males with severe uveitis at diagnosis was higher (55% of 22, OR: 3.5; 95% CI: 1.4–8.3; p = 0.006), and male gender was one factor independently associated with severe disease at diagnosis (OR: 3.7; 95% CI: 1.3–10.7).

In the present study, we found that PLT, CRP, and ESR1 correlated significantly with the severity of the disease while other laboratory parameters had no significant correlation with the severity of the disease. In agreement with our results, Huang et al., 2013 (52) showed that ESR is a useful marker for monitoring disease activity. Also, Sarkar et al., 2017 (53) found that the patients with high disease activity reflected as high JADAS27, all had elevated inflammatory markers at the time of recruitment. Güneş et al., 2015 (54) found that there were no statistically significant differences in WBC and PDW values between JIA patients with active disease and those with disease remission. Plt count was elevated during the active disease phase of JIA compared with the remission phase.

Furthermore, Zhou and Gu, 2019 (55) showed that the number of joints showing synovitis at baseline was positively correlated with CRP, ESR, number of joints with active disease.

Contrarily, Riaaz et al. 2020 (56) and Sarkar et al., 2017 (53) found a significant relationship between disease activity with anemia in JIA patients. All the patients with severe disease activity were anemic.

In the present study, MTX, Pulse steroid, Actemra, and Lefluonamide usage differed significantly according to the severity of the disease while Humera, Endoxan, Enbrel, and NSIAD show no significant differences. Nordal et al 2012 (28) agreed with our results that a high mean JADAS score during the disease course was significantly associated with DMARD treatment in a prospective, longitudinal, multi-center Nordic JIA cohort.

The main limitation is that it was conducted in a single center and included a limited number of patients, with the sample size in analyses further reduced upon patient stratification

Conclusion

The types of JIA differ significantly from each other as regards fever, rash, and organomegaly with an increase in systemic onset rather than other types. However, ophthalmic affection shows no significant difference between JIA subtypes. A low percentage of cases had uveitis indicating low severity of disease in the studied cases. Biological treatment was given to severe and resistant cases when indicated. Regular investigations help in decreasing drug complications and easy assessment of patients with drug resistance or remission.

Abbreviations

AC	**anterior chamber**
ACR	American College of Rheumatology
ANA	Antinuclear Antibody
CCP	Cyclic Citrullinated Peptide
CRP	C-reactive protein
DMARD	disease-modifying antirheumatic drugs
ERA	enthesitis-related arthritis
ESR	erythrocyte sedimentation rate
HLA	human leukocyte antigen
IAC	Intra-articular corticosteroid
IL	interleukin
ILAR	International League of Associations for Rheumatology
JCA	juvenile chronic arthritis
JIA	Juvenile idiopathic arthritis
JIA-U	Juvenile idiopathic arthritis associated uveitis
jPsA	Juvenile Psoriatic arthritis
MAS	Macrophage Activation Syndrome
MCP	metacarpophalangeal
MMF	mycophenolate mofetil
MTP	metatarsophalangeal
MTX	Methotrexate
PCR	polymerase chain reaction
PGA	physician's global assessment of disease activity
RCTs	randomised controlled trials
ReACCh-Out	Research in Arthritis in Canadian Children emphasizing Outcomes
RF	Rheumatoid factor
sJIA	Systemic JIA
SUN	The Standardisation of Uveitis Nomenclature
TMJ	temporomandibular joint

TNF	Tumor Necrosis Factor
VA	visual acuity
VAS	visual analogue scale

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board (IRB) of Mansoura University, and informed consent was obtained from the children's parents.

Consent for publication

Each author listed on the manuscript has approved the submission of the manuscript.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions:

Ahmed M El-Refaey: Write the manuscript and share in medical statistics and study design.

Neven Nashat Sobh: Collecting data and sharing in manuscript writing.

Dina Shahin: share in manuscript writing and study design

Ahmed Darwish: share in manuscript writing and collecting data

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