Juvenile Idiopathic Arthritis in Jordan: Single-Center Experience

Raed Alzyoud (raedalzyoud@gmail.com)
Queen Rnia Children's Hospital https://orcid.org/0000-0002-4972-5809
Motasem O. Alsuweiti
Queen Rania Pediatric Hospital: Queen Rania Children's Hospital
Heba Q. Almaaitah
Queen Rania Pediatric Hospital: Queen Rania Children's Hospital
Bushra N. Aladaileh
Queen Rania Pediatric Hospital: Queen Rania Children's Hospital
Mohammad K. Alnoubani
Queen Rania Pediatric Hospital: Queen Rania Children's Hospital
Adel M. Alwahadneh
Queen Rania Pediatric Hospital: Queen Rania Children's Hospital

Research article

Keywords: Juvenile Idiopathic Arthritis, Oligoarticular, ANA, Uveitis

Posted Date: November 12th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-103495/v1

Version of Record: A version of this preprint was published at Pediatric Rheumatology on June 12th, 2021. See the published version at https://doi.org/10.1186/s12969-021-00572-8.

Abstract

Background: Juvenile idiopathic arthritis (JIA) is a heterogeneous group of disorders, including all forms of arthritis, begin in children who are less than 16 years old. This study aims to evaluate the clinical and laboratory features of JIA in Jordanian children in a single center.

Methods: A retrospective analysis of the medical records of pediatric patients who were diagnosed as JIA based on the International League of Associations for Rheumatology (ILAR) criteria from 2015 through 2019 at a pediatric Rheumatology clinic in Queen Rania Children Hospital. All patients were below the age of 14 at the time of diagnosis. Collected data included age, gender, age at initial presentation and diagnosis, JIA subtypes, and laboratory data.

Results: A total of 210 patients were included in this cohort (94 males and 116 females) with a mean age at diagnosis 5.33 ± 3.4 years and the mean age at onset of the disease was 5.08 ± 3.4 years (range 7 months – 14 years). Oligoarticular JIA was the commonest subtype (54.7%), followed by systemic arthritis (17.1%), polyarticular (12.3%). ANA was positive in 70 patients (33.6%). Uveitis occurred in thirty (14.2%) patients

Conclusion: To the best of our knowledge, this cohort is the first report on JIA in Jordan, in comparison with other regional and international published reports, Oligoarticular JIA found to be the most common Subtype in our experience. To have more details about JIA characteristics, a population-based rather than a single-center study needs to be conducted in Jordan

Background

Juvenile idiopathic arthritis (JIA) is an inflammatory disorder characterized by chronic arthritis and is not a single disease, but it includes all forms of arthritis that begin in a child younger than 16 years of age, and last more than 6 weeks, with an unknown cause. JIA is still the most common disabling chronic rheumatic disease in children [1].

Juvenile idiopathic arthritis has been classified by ILAR (International League of Associations for Rheumatology) to seven subtypes including systemic, oligoarticular, polyarticular rheumatoid factor (RF) positive and RF negative, enthesitis-related arthritis (ERA), psoriatic, and “other” JIA [2]. Published reports on JIA showed variable order in JIA subtypes, oligoarticular JIA (27–56%), polyarticular RF negative JIA (11–28%), systemic JIA (4–17%), and ERA (3–11%) are the most common JIA subtypes [3]. There are few reports from the Middle East describing JIA among Arab children.

The purpose of this study is to describe JIA patterns in Jordanian children in a single center and to compare them with international and regional data.

Methods

A retrospective analysis of confirmed JIA cases based on ILAR classification criteria [2], at Queen Rania Children's Hospital, Rheumatology Division during the period from 2015 till 2019.

Patients who had arthritis due to other than Juvenile idiopathic arthritis were excluded from the study. Collected data were tabulated and included: gender, age at disease onset, patient age at the time of diagnosis, joint involvement at presentation, JIA subtype, Antinuclear antibody (ANA), rheumatoid factor (RF), uveitis, and treatment options. ANA was determined by indirect immunofluorescence using Hep-2 cell, and titers > 1/80 were considered positive. RF was studied on nephelometry and considered positive when titers were ≥ 15 units/mL. The RF-positive disease was determined by the attainment of at least two positive results, 3 months apart, in the first 6 months of observation. All patients had screened for uveitis, frequency of visits based on uveitis risk, screening by slit-lamp examination at dedicated uveitis clinic.

For the analysis of continuous outcome data, we used the ANOVA test with post-hoc analysis using the Tukey correction. For assessing the distribution of categorical variables, we used the Pearson's Chi-square test, Fisher's exact test, and odds ratios (OR). Results were considered significant for a p-value of less than 0.05. Statistical analysis was done using the Statistical Program for Social Science (SPSS) version 18.0 (Armonk, NY). The study has been approved by the Royal Medical Services Ethical Committee.

Results

A total of 210 JIA patients were included in this study; 94 (45%) males and 116 (55%) females (male to female ratio 1:1.2). The mean age at diagnosis was 5.45 ± 3.4 years ranged from 7 months to 14 years. Twenty-four patients (22.5%) had a positive family history of Rheumatoid arthritis as shown in table 1.

ILAR classification of our cohort is shown in table 2; the most frequent JIA was oligoarthritis (54.7% n= 115), followed by systemic arthritis (17.1% n=36), polyarthritis (12.3% n=26), psoriatic arthritis (8.5% n=18), and enthesitis-related arthritis (7.1% n=15).

Oligoarticular JIA was the commonest subtype in 115 patients (54.7%), with a female predominance 76 patients (66%) and male to female ratio 1: 1.94. The age of disease onset ranged between 10 months to 14 years (mean 5.0 ± 3.2 years), mean age at diagnosis 5.25 ±3.2 years.

The mean age of disease onset differed significantly between JIA subtypes ($p<0.01$), with Oligoarthritis and Systemic arthritis having an earlier onset (Figure 1).

Oligoarticular JIA patients were subclassified into persistent oligoarticular JIA ninety-six patients (84%), and 19 patients (16%) with extended oligoarticular JIA. Thirty-six patients (17.1%) were allocated to systemic JIA, which was observed to be the second most frequent subtype, of them 20/36 (56%) were males and 16/36 (44%) females. Fever and arthritis were the universal findings in all patients with systemic arthritis, twenty-four patients (66%) had a skin rash.

Positive Antinuclear antibody (ANA) was present in 70/210 (33.6%), and occurred more in Oligoarticular subtype 25/115 (21.7%) with female predominance 53 (76.6%), and was also found positive in Systemic arthritis in 3/36 patients (8.3%).

Uveitis was reported in 30 (14.2%) most of them were Oligoarticular JIA 25/115 (21.7%) and was associated with positive ANA in 16/115 (14%).

The patterns of joint involvement at the time of presentation associated with extra-articular manifestations are listed in (table 3). The most common joint involved in the presentation was the knee which occurred in almost all oligoarticular, polyarticular and systemic arthritis, ankle arthritis was the second most common in oligoarticular JIA 50/210 (24%) followed by elbow 38/210 (18%).

(Figure 2) demonstrates the distribution of the most common articular manifestation in the commonest JIA subtypes.

In systemic arthritis, wrist arthritis was the second common joint involved 20/36 (55.5%) followed by the ankle in 18/36 (50%), systemic manifestations: fever occurred in all patients, skin rash 24/36 (66.6%) and lymphadenopathy and serositis were reported in two patients for each (5.5%).

We calculated the distribution of articular and extraarticular clinical manifestations (see Table 3) for Oligoarticular, Polyarticular, and Systemic JIA. We only compared the manifestations where we had at least one recorded case for each subgroup, meaning: Elbow, Wrist, Knee, Ankle, and Uveitis. Pearson's Chi-square test shows a significant difference in the distribution of symptoms between the groups ($p<0.05$).

Odds ratio (OR) was computed for each subgroup pair (Oligo-JIA/Poly-JIA; Oligo-JIA/Systemic JIA; Poly-JIA/Systemic JIA). We applied Fisher's exact test for independence and we reported the p-value, OR, and OR 95% confidence interval (CI) presented in Table 4.

Elbow manifestations were independent of the subgroups ($p>0.05$). Wrist manifestations were dependent on the subgroups for Oligo-JIA/Systemic JIA and Poly-JIA/Systemic JIA ($p<0.0001$). Patients with systemic JIA had higher odds of developing wrist manifestations than patients with oligo and poly-JIA. Knee manifestations were dependent on the Oligo-JIA/Poly-JIA and Oligo-JIA/Systemic JIA subgroups ($p<0.05$). Patients with oligo-JIA had lower odds of developing these symptoms compared to the other subgroups. For ankle and uveitis manifestations, a dependence on subgroups was observed only in the Oligo-JIA/Systemic JIA category ($p<0.001$), with ankle manifestations being more common for the systemic JIA and uveitis in the oligo-JIA.

Pharmacological treatments for patients during the study period are listed in the table (4); Nonsteroidal anti-inflammatory drugs (NSAIDs) were used in 174/210 (82.8%), steroids 191/210 (91%) oral 160 (76.1%), IV 33 (15.7%) and Intra-articular 136 (64.7%), Disease-modifying anti-rheumatic drugs (DMARDs) were used in 198/210 (94.2%), and methotrexate was the commonest DMARD used in 171/210 (81.4%). Biological treatment was used in 105/210 (50%), Infliximab was used in 30/210 (14.2%).

Discussion

Pediatric Immunology and Rheumatology Division at Queen Rania Children Hospital, King Hussein Medical Center, Amman, Jordan, which is the only center in the country has dedicated to pediatric autoimmune disorders, rheumatological disorders, and immune dysregulations, this retrospective study was conducted.

This study aims to describe the clinical characteristics of JIA patients and to characterize our community's clinical characteristics of the disease. To the best of our knowledge, this is the first single-center study that describes the pattern of JIA in Jordanian children.

As in previous similar studies, Oligoarticular JIA was the most common subtype, as in Spain (51%), Sweden (44.7%) and Turkey (41%) [4, 5, 6] the Oligoarticular in our cohort was the most common JIA subtype 115/210 (54.7%), Middle East and North Africa (MENA) data showed that Oligoarticular JIA is also the most common subtype as reported in Lebanon (31%), Iraq (48%), Saudi Arabia (40.5%) and Egypt (41.3%) [7, 8, 9, 10].

Unlike similar studies published in Oman and Tunisia where Polyarticular JIA is the most common subtype 46.7%, 66% respectively [11, 12], whereas systemic juvenile arthritis (36.5%) was the most common subtype in another study from Saudi Arabia [13]. Table 6 summarizes the published data on JIA patterns in different countries.

The current study reports that the mean age at disease onset was 5.13 ± 3.4 years (range from 7 months to 14 years) which was much lower than that reported by Abou El-Soud et al 10.5 ± 3.6 (range 4–15) years [14], and was close to data published by Bahabri S et al (6 years) [15], and lower than patients of European origin as published by Saurenmann et al 6.5 years (6.1–6.8 years) [16] this observation might be explained by the lower range of the pediatric population of our cohort, as pediatric patients are seen till the age of 14 years at our hospital, then they have referred to adult service. The current study showed female predominance 116/210 with a male to female ratio 1:1.2, a higher ratio was published by E. Solau-Gervais et al, 1:1.7 [17].

Antinuclear antibody (ANA), was positive in 33.6% of cases. Although others such as Khuffash et al [18] and Ozdogan et al [19] mentioned lower results (12%, 5% respectively). This observation reflected on the increased incidence of uveitis. Among oligoarticular JIA cases, the number of ANA-positive patients was 61/115 (53%), which was Close to a study conducted by Al Wahadneh et al 50% [20].

Oligoarthritis is overwhelmingly a disease of the lower limbs, with the knee joint for the most part affected, trailed by the lower limbs with ankle most affected. [21] Similar to the international data the Pattern of joint involvement in Oligoarticular JIA in our cohort showed a predominance of lower limb involvement with knee and ankle involved in 100%, 17.8% respectively, similar joint involvement was found in polyarticular JIA with knee and ankle were involved in 100%, 66.6% respectively. In our dataset,

elbow, knee, ankle, and uveitis manifestations were more common in patients with oligo JIA (Fig. 2). When comparing these manifestations between pairs of the 3 subgroups, we concluded that elbow manifestations were not significantly influenced by the subgroups, while wrist, ankle, knee, and uveitis manifestations were dependent on the subgroups compared. Lower odds of presenting wrist, knee, and ankle manifestations were seen in oligo JIA, while uveitis had higher odds in being present in these patients.

Extra-articular manifestations in systemic-onset JIA was fever and reported in 100%, followed by skin rash 66.6%, and the pattern of joint involvement showed upper and lower joints involvement with knee and ankles arthritis reported in 100% and 50%, while elbow and wrist involvement 28% and 55.5% of cases. When comparing these findings with other published data in Egypt [22], we reported a higher incidence of both extra-articular and articular manifestations in systemic-onset JIA.

Uveitis reported in 30/210 (14.2%) and was close to results published by Angeles-Han et al 11.6%. [23]. Oligoarticular was the commonest subtype complicated with uveitis 25/115 (21.7%), and positive ANA found in 16/25 (64%). According to one study from Saudi Arabia, uveitis affects 8.1% of oligoarticular JIA [24]. Another large population-based study in Germany of JIA patients; uveitis occurred in 12% of all JIA types (25% extended Oligoarticular and 16% persistent Oligoarticular) [25]. However, it is not clear if this complication is due to the high prevalence of Oligoarticular JIA or not.

Macrophage activation syndrome (MAS) is a life-threatening complication of systemic juvenile idiopathic arthritis [26], it occurred in our cohort in two patients 2/210 (0.9%), while a higher incidence (33.9%) of this serious complication was reported by Çakan et al [27].The author explained this high rate of MAS in the study by that the institute where the study conducted is a referral center for pediatric rheumatology and a high Percentage of Mediterranean fever (MEFV) gene mutation carriers which may increase the possibility of developing more autoinflammatory disorders than other healthy Population.

JIA treatment aims to reduce the pain, gain joint function, preserve muscle strength, and to avoid systemic complications [28]. Although there is no consensus on JIA treatment, but there are many guidelines released from different rheumatology societies or colleges. NSAIDs have traditionally been the mainstay treatment for all kinds of JIA during the First 4 to 6 weeks of the initial treatment either alone or with combination with Intra-articular steroid injection. In case of inadequate response; DMARD was started, and methotrexate (MTX) is the most common DMARD used, and in case of failure, no response or intolerance a switch to another DMARD or add on Biological agent is introduced. [30, 31]

Non-steroidal anti-inflammatory drugs (NSAIDs) were used in 174/210 (82.8%) oligoarticular 103/115 (89.2%), systemic JIA 35/36 (96.7%), at diagnosis or during their disease course. A higher percentage of 99% of oligoarticular JIA patients in central Italy received NSAIDs [29].

Methotrexate is cornerstone treatment in Oligoarticular, polyarticular JIA and in systemic JIA with articular inflammation predominance [32], in our cohort, MTX was used in 81.4% of cases 76.7% of

oligoarticular JIA,100% in polyarticular and 90% in systemic arthritis, while MTX was used in 66% of cases in Omani study [11]. Other DMARDs were used in cases of MTX toxicity or intolerance, leflunomide 6/210 (2.8%), Sulfasalazine 2 (0.95%), myfortic (MMF) were used in one patient, hydroxychloroquine was used in 4/210 (1.9%) of cases.

Biological treatment found to be safe and effective in severe JIA or refractory cases to synthetic DMARDs [33], in our cohort biological agents were used in 105/210 (50%), and they include Anti-TNF (Tumor necrosis factor) which is a cytokine play role in the pathogenesis of JIA and found in increased levels in the synovial fluid. Tocilizumab a monoclonal antibody directed against IL-6 receptor; increased serum levels found in systemic arthritis, Anakinra is a human recombinant IL-1 receptor antagonist and play a role in the pathogenesis of JIA and is a preferred treatment of systemic arthritis, Rituximab is a human monoclonal antibody directed against CD20 lymphocytes leading to increase B-cell apoptosis and decrease mature B cell expressing CD20 [34], anti-TNF drugs were used in our cohort in 74/210 (35.2%) in which infliximab was the commonest anti-TNF used 30/210 (14.2%), followed by Etanercept 25/210 (12%) while Adalimumab was used in 15/210 (7.1%) and Golimumab in four patients (1.9%). when compare our results in using biological DMARDs with regional data as in Saudi Arabia[9], where biological DMARDS were used in 28.4%, with adalimumab being commonest biological treatment, this difference could be explained by that our cohort is larger and the easy accessibility to biological treatment when applying the treat to target strategy. Thirty-eight patients (18%) in our cohort used more than one biological agent, and this group of patients reflects the more severe course in our cohort, and most of them switched to another biological agent due to the inefficiency of the previous agents

Tocilizumab was used in 8% (17/210 of them thirteen patients with systemic arthritis), Anakinra (IL-1 antagonist) was used in one patient (0.5%) with systemic arthritis, Rituximab was used in 8/210 (3.8%) five patients were with systemic arthritis resistant to immunosuppressive, steroid and other conventional biological treatment. A study done by E. Alexeeva et al [35] showed that rituximab may be effective in severe systemic arthritis that is resistant to immunosuppressive treatment and glucocorticoid therapy and other biological treatment.

Conclusions

To the best of our knowledge, this is the first study in Jordan describing the pattern of JIA, realizing that our hospital is the country's leading tertiary clinic for pediatric rheumatology, and these results show the pattern of JIA in Jordanian children's of being oligoarticular JIA the commonest subtype as in some Middle East and European countries, and unlike JIA pattern in Arab gulf countries and North Africa.

Our study limitations include the nature of being a retrospective study and is based on single-center rather than papulation based which may give more details about JIA characteristics and that it may not include "mild cases" that have not been referred to our hospital or missed diagnosed, another limitation that we cannot include patients with JIA who were more than 14 years of age at disease onset due to governmental policies of age cutoff, where is the age defined by ILAR classification is up to 16 years.

Abbreviations

JIA: Juvenile Idiopathic Arthritis.

ILAR: International League of Associations for Rheumatology.

ANA: Antinuclear Antibody

RF: Rheumatoid Factor

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

DMARD: Disease-Modifying Anti-Rheumatic Drugs

MMF: Mycophenolate Mofetil.

MTX: Methotrexate

Declarations

Ethics approval and consent to participate: Not applicable

The study has been approved by Royal Medical Services Ethical Committee, Order number 9/2020 on Septmber,1st, 2020.

Consent for publication: Not applicable

Availability of data and material:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

All authors have no competing conflicts to declare.

Funding:

Neither authors nor the research project had received any research grants, or fund by the Royal Medical Services directorate or other funders.

Authors' contributions:

All authors read and approved the final manuscript, participated in the study design and coordination, statistical analysis, and helped to draft the manuscript.

Acknowledgements:

All authors would thank the medical staff in Immunology, Allergy and Rheumatology Division at Queen Rania Children's Hospital, as well as patients' families

References

1. Gabriella Giancane. Alessandro Consolaro, Juvenile Idiopathic Arthritis: Diagnosis and Treatment, Rheumatol Ther (2016) 3:187–207 DOI 10.1007/s40744-016-0040-4
2. Ross E Petty, Taunton R Southwood, International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001.J Rheumatol 2004;31;390-392
3. Ravelli, A., & Martini, A. (2007). Juvenile idiopathic arthritis. Lancet. https://doi.org/10.1016/S0140-6736(07)60363-8
4. Modesto, C., Antón, J., Rodriguez, B., Bou, R., Arnal, C., Ros, J., … Barceló, P. (2010). Incidence and prevalence of juvenile idiopathic arthritis in Catalonia (Spain). Scandinavian Journal of Rheumatology. https://doi.org/10.3109/03009741003742722
5. Berthold, E., Månsson, B., & Kahn, R. (2019). THU0526 LONG-TERM OUTCOME IN JUVENILE IDIOPATHIC ARTHRITIS – A POPULATION-BASED STUDY FROM SWEDEN. Annals of the Rheumatic Diseases, 78(Suppl 2), 554 LP – 555. https://doi.org/10.1136/annrheumdis-2019-eular.1579
6. Demirkaya, E., Özen, S., Bilginer, Y., Ayaz, N. A., Makay, B. B., Ünsal, E., … Türker, T. (2011). The distribution of juvenile idiopathic arthritis in the eastern Mediterranean: Results from the registry of the Turkish paediatric rheumatology association. Clinical and Experimental Rheumatology.
7. Dagher R, Assi S. Juvenile idiopathic arthritis: a single-center Lebanese study. Pediatr Rheumatol Online J. 2014;12(Suppl 1):P179. Published 2014 Sep 17. doi:10.1186/1546-0096-12-S1-P179
8. Naser WE. Assessment of the quality of life of Iraqi children with juvenile idiopathic arthritis: A single-center study. Med J Babylon 2019;16:65-9
9. Alqahtani, Y. A. M. (2020). The patterns of juvenile idiopathic arthritis. Bahrain Med Bull 2020; 42 (3): 171 - 175.
10. S, Salah & A, Hamshary & Lotfy, Hala & Rahman, H.. (2009). Juvenile Idiopathic Arthritis, the Egyptian Experience. Journal of Medical Sciences. 9. 10.3923/jms.2009.98.102
11. Abdwani, R., Abdalla, E., Al Abrawi, S. et al. Epidemiology of juvenile idiopathic arthritis in Oman. Pediatr Rheumatol **13,** 33 (2015) doi:10.1186/s12969-015-0030-z
12. Alaya Z, El Amri N, Zaghouani H, et al AB1030 Juvenile Idiopathic Arthritis in Central Tunisia: Clinical and Therapeutic Features (About 54 Cases) Annals of the Rheumatic Diseases 2015;**74:**1243.
13. Al-Hemairi, M. H., Albokhari, S. M., & Muzaffer, M. A. (2016). The Pattern of Juvenile Idiopathic Arthritis in a Single Tertiary Center in Saudi Arabia. International Journal of Inflammation. https://doi.org/10.1155/2016/7802957

14. Abou El-Soud, A. M., El-Najjar, A. R., El-Shahawy, E. E., Amar, H. A., Hassan, T. H., Abd-Allaha, S. H., & Ragab, H. M. (2013). Prevalence of juvenile idiopathic arthritis in Sharkia Governorate, Egypt: Epidemiological study. Rheumatology International. https://doi.org/10.1007/s00296-013-2707-2
15. Bahabri, S., Al-Sewairi, W., Al-Mazyad, A., Karrar, A., Al-Ballaa, S., El-Ramahai, K., & Al-Dalaan, A. (1997). Juvenile rheumatoid arthritis: The Saudi experience. Annals of Saudi Medicine. https://doi.org/10.5144/0256-4947.1997.413
16. Saurenmann, R. K., Rose, J. B., Tyrrell, P., Feldman, B. M., Laxer, R. M., Schneider, R., & Silverman, E. D. (2007). Epidemiology of juvenile idiopathic arthritis in a multiethnic cohort: Ethnicity as a risk factor. Arthritis and Rheumatism. https://doi.org/10.1002/art.22709
17. Elisabeth Solau-Gervais, Caroline Robin, Catherine Gambert, Sophie Troller, Sophie Danner, Bruno Gombert, Françoise Debiais, Régis Hankard, Prevalence and distribution of juvenile idiopathic arthritis in a region of Western France. oint Bone Spine. 2010 Jan; 77(1): 47–49. doi: 10.1016/j.jbspin.2009.11.002
18. Khuffash FA, Majeed HA. Juvenile rheumatoid arthritis among Arab children. Scand J Rheumatol2006; 17: 393-395
19. 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.
20. Al Wahadneh, A.M., Abu Zeid, A.F. & Khreisat, W.H. (2007). Juvenile idiopathic oligoarthritis: analysis of 42 cases in Jordan. EMHJ - Eastern Mediterranean Health Journal, 13 (2), 461-464, 2007
21. Huemer C, Malleson PN, Cabral DA, Huemer M, Falger J, Zidek T, Petty RE. Patterns of joint involvement at onset differentiate oligoarticular juvenile psoriatic arthritis from pauciarticular juvenile rheumatoid arthritis. J Rheumatol. 2002 Jul;29(7):1531-5. PMID: 12136915.
22. Angeles-Han, S. T., Pelajo, C. F., Vogler, L. B., Rouster-Stevens, K., Kennedy, C., Ponder, L., … Prahalad, S. (2013). Risk markers of juvenile idiopathic arthritis-associated uveitis in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry. Journal of Rheumatology. https://doi.org/10.3899/jrheum.130302
23. Hussein, Z., Wagdy, R., Shawki, M., Zohni, S., & Shehawy, I. (2018). The pattern of juvenile idiopathic arthritis; a retrospective Egyptian study. The Egyptian Journal of Pediatric Allergy and Immunology. https://doi.org/10.21608/ejpa.2018.10417
24. Moued, M. M., Al-Saggaf, H. M., Habib, H. S., & Muzaffer, M. A. (2013). Oligoarticular juvenile idiopathic arthritis among Saudi children. Annals of Saudi Medicine. https://doi.org/10.5144/0256-4947.2013.529
25. Heiligenhaus, A., Niewerth, M., Ganser, G., Heinz, C., Minden, K., Ganser, G., … Zierhut, M. (2007). Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. Rheumatology. https://doi.org/10.1093/rheumatology/kem053
26. Ravelli, A., Grom, A. A., Behrens, E. M., & Cron, R. Q. (2012). Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: Diagnosis, genetics, pathophysiology, and treatment. Genes

and Immunity. https://doi.org/10.1038/gene.2012.3

27. Mustafa Çakan, Şerife Gül Karadağ, Ayşe Tanatar & Nuray Aktay Ayaz (2019): The frequency of macrophage activation syndrome and disease course in systemic juvenile idiopathic arthritis, Modern Rheumatology, DOI: 10.1080/14397595.2019.1660026
28. Kim, K. N. (2010). Treatment of juvenile rheumatoid arthritis. Korean Journal of Pediatrics. https://doi.org/10.3345/kjp.2010.53.11.936
29. Marzetti, V., Breda, L., Miulli, E., Filippetti, F., Mancini, C., Chiarelli, F., & Altobelli, E. (2017). Clinical characteristics of juvenile idiopathic arthritis in an area of central Italy: A population-based study. Annali Di Igiene. https://doi.org/10.7416/ai.2017.2152
30. Ringold S, Weiss PF, Beukelman T, DeWitt EM, Ilowite NT, Kimura Y, Laxer RM, Lovell DJ, Nigrovic PA, Robinson AB, Vehe RK; American Collge of Rheumatology. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. Arthritis Rheum. 2013 Oct;65(10):2499-512. doi: 10.1002/art.38092. PMID: 24092554; PMCID: PMC5408575.
31. Wallace, C. A. (2006). Current management of juvenile idiopathic arthritis. Best Practice and Research: Clinical Rheumatology. https://doi.org/10.1016/j.berh.2005.11.008
32. Ferrara, G., Mastrangelo, G., Barone, P. et al. Methotrexate in juvenile idiopathic arthritis: advice and recommendations from the MARAJIA expert consensus meeting. Pediatr Rheumatol 16, 46 (2018). https://doi.org/10.1186/s12969-018-0255-8
33. Mourão, A & Rodrigues, Ana & Vinagre, F & Sousa, Elsa & Polido-Pereira, Joaquim & Macieira, Carla & Ramos, F & Costa, J & Pedro, J & Silva, J & Fonseca, João & Santos, Maria & Canhão, Helena. (2010). Eight years of experience with biological treatment in juvenile idiopathic arthritis. Journal of Translational Medicine. 8. 1-1. 10.1186/1479-5876-8-S1-P64.
34. Kasapcopur O, Barut K. Treatment in juvenile rheumatoid arthritis and new treatment options. Türk Pediatri Arşivi. 2015;50(1):1-10.
35. Alexeeva E, Valiyeva S, Denisova R, et al FRI0338 Efficacy and safety of rituximab retreatment in refractory systemic juvenile idiopathic arthritis Annals of the Rheumatic Diseases 2013;**71:**428

Tables

Table 1: Demographics of 210 patients

	Range	Male (n=94)	Female (n=116)	Total (n=210)
Age at disease onset (mean)	7 mo - 14 yr	5.42 ± 3.3 yr	4.90 ± 3.4 yr	5.08 ± 3.4 yr
Age at diagnosis (mean)	8 mo - 14 yr	5.77 ± 3.4 yr	5.0 ± 3.3 yr	5.33 ± 3.4 yr
Consanguinity	-	24 (25%)	13 (11%)	37 (26%)
Family history of RA	-	8 (8.5%)	16 (14%)	24 (22.5%)

Yr- years, mo- months, RA- rheumatoid arthritis

Table 2: distribution of JIA subtypes

JIA subtype	n (%)	Gender		Age of onset (yr)	
		Male	Female	Range	Mean
Oligoarthritis	115 (54.7%)	39 (34%)	76 (66%)	10 mo- 14yr	5.0 ± 3.2 yr
R.F (-) polyarthritis	18 (8.5%)	6 (33%)	12 (66%)	4 yrs -12 yr	8.0 ± 3.2 yr
R.F (+) polyarthritis	8 (3.8%)	2 (25%)	6 (75%)	4 yrs -12 yr	8.0 ± 3.2 yr
Systemic arthritis	36 (17.1%)	20 (56%)	16 (44%)	9 mo- 13 yr	3.8 ± 2.7 yr
Enthesitis-related arthritis	15 (7.1%)	9 (60%)	6 (40%)	6 yr- 12 yr	10 ± 1.77 yr
Psoriatic arthritis	18 (8.5%)	10 (56%)	8 (44%)	7 mo- 11 yr	5.5 ± 3.9 yr

JIA- Juvenile Idiopathic Arthritis, RF- Rheumatoid factor, mo-months, yr-years

Table 3: Articular and extraarticular clinical manifestations at presentation				
	Oligo JIA n (%)	Polyarticular JIA n (%)	Systemic JIA n (%)	P-value
TMJ	4 (3.4%)	0 (0%)	0 (0%)	n/a
Cervical	0 (0%)	0 (0%)	0 (0%)	n/a
Shoulder	0 (0%)	0 (0%)	0 (0%)	n/a
Elbow	24 (21%)	4 (15%)	10 (28%)	0.48
Wrist	14 (12%)	3 (11.5%)	20 (55.5%)	<0.001
MCP	0 (0%)	4 (15%)	1 (2.7%)	n/a
PIP	1 (0.8%)	3 (11.5%)	2 (5.5%)	n/a
Hip	2 (1.6%)	1 (4%)	0 (0%)	n/a
Knee	92 (80%)	26 (100%)	36 (100%)	<0.001
Ankle	24 (21%)	8 (30%)	18 (50%)	<0.01
Fever	0 (0%)	0 (0%)	36 (100%)	n/a
Rash	0 (0%)	0 (0%)	24 (66.6%)	n/a
LNE	0 (0%)	0 (0%)	2 (5.5%)	n/a
HSM	0 (0%)	0 (0%)	0 (0%)	n/a
Serositis	0 (0%)	0 (0%)	2 (0%)	n/a
Uveitis	25 (21.7%)	3 (11.5%)	1 (2.7%)	0.02
MAS	0 (0%)	0 (0%)	2 (5.5%)	n/a
p-values are based on the Chi-square test performed to assess the difference in the distribution of each manifestation between the subgroups. n/a – not applicable – where there were not enough cases in each subgroup to perform the analysis. p is significant for less than 0.05				

Table 4 – Odds ratios between the subgroups for extraarticular manifestations

	Oligo JIA/Poly JIA			Oligo JIA/Systemic JIA			Poly JIA/Systemic JIA		
	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI
Elbow	0.78	1.45	0.45-4.61	0.37	0.685	0.29-1.61	0.35	0.472	0.12-1.72
Wrist	1	1.063	0.28-4.006	<0.0001	0.11	0.046-0.262	0.0005	0.104	0.026-0.411
Knee	0.007	0.07	0.004-1.26	0.002	0.053	0.003-0.91	1	0.726	0.013-37.81
Ankle	0.3	0.59	0.23-1.52	0.001	0.26	0.119-0.583	0.19	0.44	0.15-1.28
Uveitis	0.28	2.130	0.59-7.67	0.009	9.722	1.26-74.55	0.3	4.565	0.44-46.64

CI, confidence interval; JIA, juvenile idiopathic arthritis; OR, odds ratio.

p-values represent the results of Fisher's exact test applied for each manifestation between two groups. A $p<0.05$ was considered significant and show that in our dataset, the extraarticular manifestation and the subgroups are dependent.

Table 5: Pharmacological Treatment used in all JIA subtypes						
Subtype **Drug**	**Oligoarticular**	**Polyarticular**	**Systemic JIA**	**Psoriatic JIA**	**Enthesitis Related**	**Total (%)**
NSAIDs	102	9	34	15	14	174 (82.8%)
steroid	110	17	36	15	8	191 (91%)
oral	84	17	36	15	8	160 (76.1)
IA	96	8	26	4	2	136 (64.7%)
IV	6	8	17	2	0	33 (15.7%)
MTX	87	26	32	18	8	171 (81.4%)
HCQ	4	0	0	0	0	4 (1.9%)
MMF	1	0	0	0	0	1 (0.5%)
leflunomide	4	0	0	0	2	6 (2.8%)
Cyclosporine	0	0	5	2	0	7 (3.3%)
Sulfasalazine	2	0	0	0	0	2 (0.95%)
Infliximab	12	5	6	3	4	30 (14.2%)
Etanercept	14	0	2	7	2	25 (12%)
Adalimumab	12	0	2	1	0	15 (7.1%)
Tocilizumab	2	0	15	0	0	17 (8%)
Anakinra	0	0	1	0	0	1 (0.5%)
Rituximab	0	2	5	1	0	8 (3.8%)
Golimumab	2	2	0	0	0	4 (1.9%)
Secukinumab	0	0	0	3	2	5 (2.3%)

Due to technical limitations, table 6 is only available as a download in the Supplemental Files section.

Figures

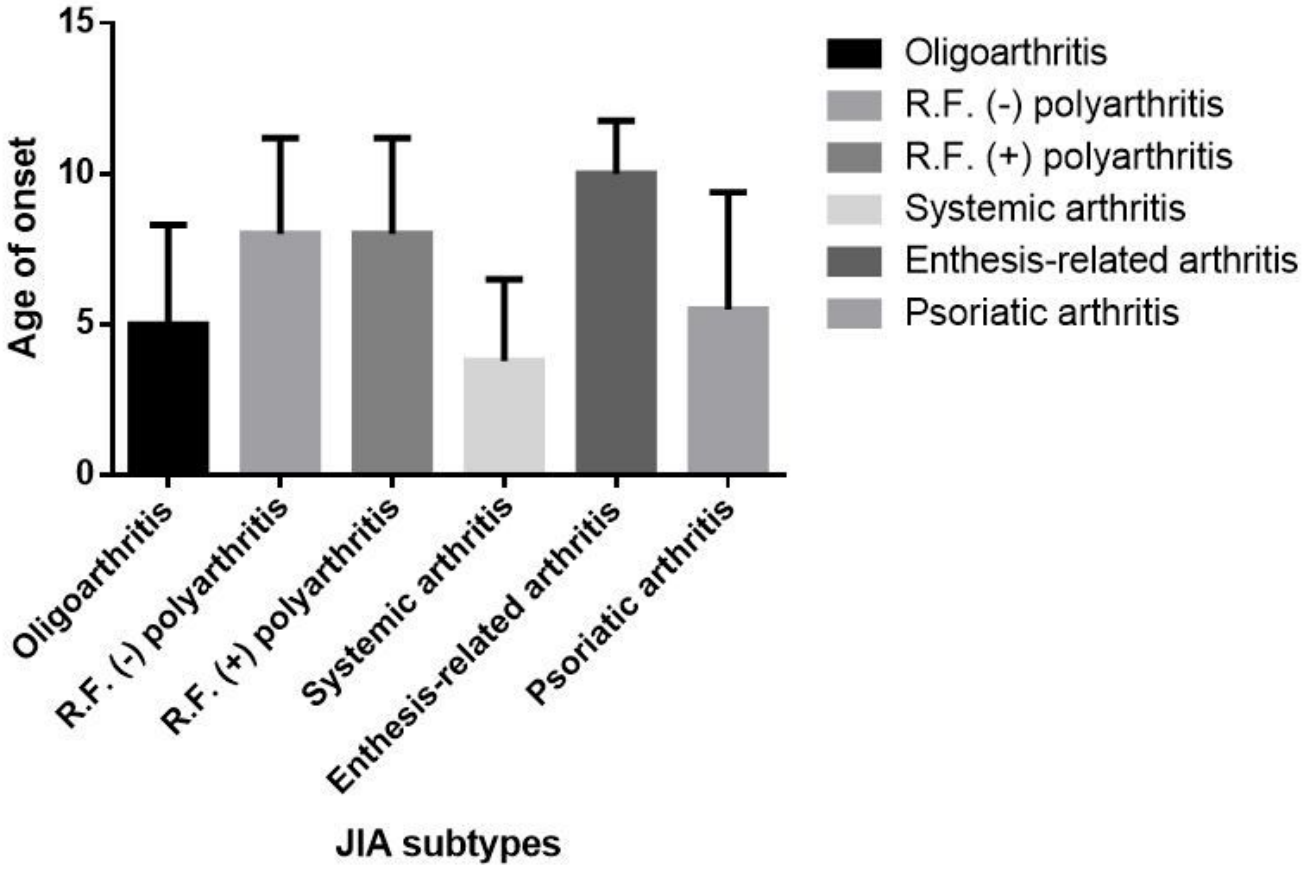

Figure 1

The mean age of disease onset differed significantly between JIA subtypes ($p<0.01$), with Oligoarthritis and Systemic arthritis having an earlier onset (Figure 1).

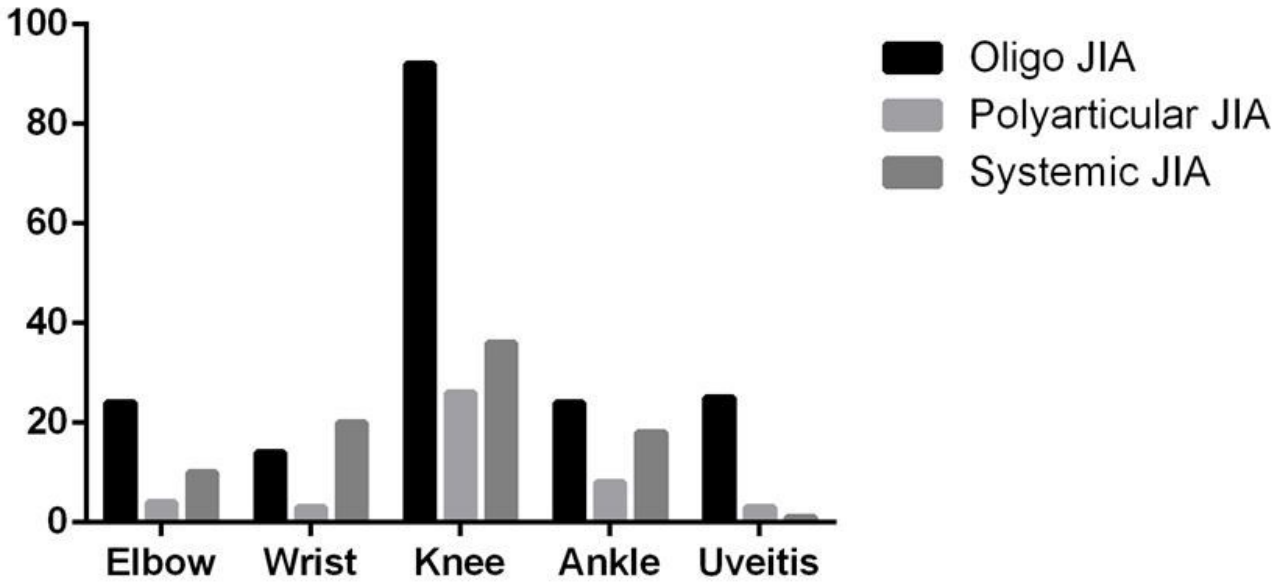

Figure 2

(Figure 2) demonstrates the distribution of the most common articular manifestation in the commonest JIA subtypes.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table6.JPG