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Running head: Impact of COVID-19 lockdown on children with JIA

Increased relapse rate during COVID-19 lockdown in an Italian cohort of children with juvenile idiopathic arthritis

Roberta Naddei MD[1], Renata Alfani MD[1], Martina Bove MD[1], Valentina Discepolo MD PhD[1], Filomena Mozzillo MD[1], Alfredo Guarino MD[1], Maria Alessio MD[1]

[1] Department of Translational Medical Sciences, Pediatric Section, University of Naples Federico II, Naples, Italy.

Correspondence to:

Maria Alessio, Department of Translational Medical Sciences, Pediatric Section, University of Naples Federico II, Via Sergio Pansini n. 5, 80131, Naples, Italy.

Telephone number: +390817463269; Fax number: +390817464230, email: alessio@unina.it.

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Abstract

Objectives: Changes of routine disease management associated with COVID-19 lockdown might have potentially affected the clinical course of juvenile idiopathic arthritis (JIA). Aim of our study was to assess the rate of disease flare before and during COVID-19 lockdown to investigate its impact on disease course in JIA children.

Methods: A single-center retrospective study was conducted, including patients presenting inactive JIA between September 1st, 2018 and March 9th, 2019 (group A) and between September 1st, 2019 and March 9th, 2020 (group B). For each patient, demographic and clinical data were collected. The rate of JIA flare from March 10th, 2019 to June 30th, 2019 for group A and from March 10th, 2020 to June 30th, 2020 for group B was compared.

Results: Group A included 126 patients and group B 124 patients. Statistical analysis did not show significant differences among the two cohorts with respect to age, sex, age of JIA onset, JIA subtype, co-occurrence of uveitis, ANA positivity and past or ongoing medications. The rate of disease flare during lockdown at time of first COVID-19 pandemic wave, was significantly higher in comparison to the previous year (16.9% vs 6.3%, p=0.009).

Conclusion: Our study showed that COVID-19 lockdown was associated with a higher rate of joint inflammation in JIA children. This finding has a considerable clinical implication, since restrictive measures may be necessary in order to contain pandemics. Our data highlight the need for rearrangement in the home and healthcare management of JIA children during lockdowns.

Significance and Innovations

- In this population of children with juvenile idiopathic arthritis from Southern Italy, we observed that COVID-19 lockdown was associated with a higher rate of disease flare.
- Our data underlie the need for reconsidering home and healthcare management of children with chronic arthritis during lockdowns aimed to contain pandemics.

Introduction

The first European country affected by the Coronavirus Disease 2019 (COVID-19) pandemic was Italy, where the outbreak exploded in February 2020 having immediately far-reaching health and social implications. Since the beginning of COVID-19 outbreak, restrictive measures were implemented to prevent the spreading of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). During the so-called "phase 1" of the COVID-19 outbreak in Italy, starting on March 10th, 2020, school's closure was a major component of social distancing along with the shutdown of all non-essential activities, including leisure and sport. During "phase 2", from May 4th to June 15th, 2020, there was a progressive easing of the containment measures although schools and gyms remained closed. While national and regional governments ordered the discontinuation of deferrable medical and surgical activities during phase 1, they were allowed in phase 2.

Children affected by juvenile idiopathic arthritis (JIA) might be considered a vulnerable population. In the first months of COVID-19 pandemic, JIA patients and their parents had to cope with major challenges in the routine disease management, such as limiting non-essential health care visits and physical activity due to home confinement and the concerns raised by the use of immunosuppressive medications, like conventional disease-modifying antirheumatic drugs (cDMARDs) and biologic disease-modifying drugs (bDMARDs) (1). These factors might potentially contribute to disease worsening during the pandemic. Current findings on the course of inflammatory rheumatic diseases during lockdown mainly regard adult patients (2-4), while physical effects of pandemic on pediatric chronic arthritis (5) have not been widely reported. Therefore, we investigated the rate of JIA flare before and during COVID-19 lockdown, in order to explore its impact on disease course in children with JIA.

Methods

A single-center retrospective study was conducted by reviewing medical records of JIA patients admitted at the Pediatric Rheumatology Unit of the University of Naples Federico II with a minimal follow-up duration of 6 months. All patients were diagnosed according to the International League of Associations for Rheumatology criteria (6) and were divided in two groups:

- Group A (N=126): Patients with inactive disease (ID) between September 1st, 2018 and March 9th, 2019 (V1) and then re-evaluated between March 10th, 2019 and June 30th, 2019 (V2);
- Group B (N=124): Patients with ID between September 1st, 2019 and March 9th, 2020 (V1) and then re-evaluated between March 10th, 2020 and June 30th, 2020 (V2).

ID was defined, according to the Wallace criteria (7), as no joint with active arthritis, no systemic manifestations due to JIA, no active uveitis, normal acute-phase reactants, physician global assessment (PGA) indicating no disease activity (defined as score of 0 on a 0-10 visual analogue scale) and duration of morning stiffness <15 minutes. However, the full set of Wallace criteria could not be applied before 2020, due to the limitations in the direct medical visits which precluded PGA. In those circumstances, when the other Wallace criteria were met, the absence of disease activity was inferred through the review of the patient chart by consensus of three investigators (RN, RA and MA). Also, patients evaluated with telemedicine tools during COVID-19 lockdown and reporting no signs of active disease were included in group B (N=31). In fact, during COVID-19 lockdown, remote consultations (telephone or email interviews) were performed with patients' parents, investigating the occurrence of signs and symptoms consistent with JIA flare (morning stiffness, joint swelling and/or pain and/or limited range of motion). If any of those was present, in person consultation was ordered. Otherwise, the direct visit was deferred. For the purpose of the analysis and in agreement with Beukelman et al. (8), patients were grouped in the functional phenotypes of oligoarthritis (4 or fewer affected joints), polyarthritis (5 or more affected joints), systemic arthritis (sJIA), and enthesitis-related arthritis (ERA). Among patients with sJIA, only patients with a history of chronic arthritis that persisted in spite of inactive systemic features, were included. In order to investigate lockdown effects only on articular symptoms in JIA children, patients with active uveitis without active arthritis at V2 were excluded from the analysis. A subset of patients included in group A was also evaluated the following year in the same period and thus included also in group B (N=71).

For each patient, demographic data, JIA subtype, age at JIA onset, co-occurrence of uveitis, anti-nuclear antibody (ANA) positivity, disease duration and past therapeutic regimens were collected into a dedicated anonymized database. Date of disease onset was defined as the date when the first symptoms of arthritis were noted, as recorded in the clinical charts. For each consultation, PGA, presence of morning stiffness, presence of JIA flare including the number and type of active joints (swelling or both tenderness and limited range of motion), erythrocyte sedimentation rate, routine

out-of-school physical activity (defined as regular sport activity at least twice a week), ongoing medications and therapeutic decisions at the visit were also collected. Type of consultation (in person or remote), missed days of school and deferred medical visits were also recorded for patients undergoing V2 during COVID-19 pandemic. Medication adherence was assessed by parental report, including overall adherence (yes/no) and potential barriers. In flaring patients of group B, contact history with COVID-19 cases, suspected or confirmed COVID-19 diagnosis before JIA relapse and the results of SARS-CoV-2 serology, if available, were also investigated and collected.

The JIA relapse rate at V2 was measured and compared between patients of group A and group B. Descriptive statistics were reported as median and interquartile range (IQR) for continuous variables and as percentages for categorical ones. The rate of disease flare was expressed with 95% confidence intervals (95% C.I.). Comparison of categorical variables between the two groups were performed by χ^2 test or Fisher's exact test in case of expected frequencies less than 5, whereas Mann–Whitney U test was used in order to compare continuous variables. All statistical tests were 2-sided and considered significant with a P-value lower than 0.05.

The study protocol was approved by the Ethical Committee of the University of Naples Federico II (protocol #440/20).

Results

With regard to group A, 165 patients with JIA presented ID at V1, of those 134 underwent V2. Eight subjects affected by sJIA without persistent arthritis were excluded, resulting in a cohort of 126 patients (*figure 1*). With regard to group B, 178 patients presented ID at V1, of those 137 underwent V2. One patient with active uveitis at V2 and 12 patients with sJIA without history of persistent arthritis were excluded, resulting in a cohort of 124 patients (*figure 1*).

Looking at patients' demographic and clinical data (*table 1)*, in both groups, there was a predominance of females (77% in group A vs 75.8% in group B, p=0.826) and oligoarticular was the most frequent functional JIA phenotype (65.8% vs 62.1%, p=0.534). No significant difference was observed in regard to age at JIA onset, ANA positivity and history of uveitis (*table 1)*. Median age at V1 was 10.9 years in both cohorts; median disease duration at V1 was 5.1 and 5.3 years in group A and B, respectively (p=0.809). No difference was found in the ongoing JIA treatment at V1 (*table 1*). Twenty out of 126 patients (15.9%) presented clinical ID off medication in group A compared to 22.6% (28/124) subjects in group B (p=0.178). The proportion of patients undergoing

methotrexate (MTX) was similar (46.8% in group A vs 37.1% in group B, p=0.119), as well as the proportion of subjects treated with a bDMARD (43.7% vs 45.2%, p=0.81). Among patients on medication, therapy was tapered or discontinued in 37.7% patients of group A and 33.3% in group B at V1 (p=0.514). The proportion of children participating in out-of-school physical activities at V1 was about 54% in both cohorts (*table 1*). Altogether, these data suggest that clinical and demographic features at baseline did not differ between the two groups of patients.

Due to discontinuation of deferrable medical activities, 31/124 (25%) patients in group B were evaluated only through a remote consultation at V2, 31 (25%) had their appointment postponed for over a month. At V2, no significant difference was found with respect to the ongoing JIA treatment between the two cohorts (*table 2*). Temporary drug interruptions for greater than one week were reported in 5/81 (6.2%) in group B, four of which were unrelated to COVID-19. One patient delayed her monthly Tocilizumab infusions without medical advice, due to fear to be infected, but did not develop a flare. The parents of other 10 children expressed worries about continuing drugs for JIA during pandemic but did not report drugs discontinuation. Data on physical activity were available for 77 patients in group A: 48 (62.3%) practiced regular sport activity at V2, in comparison to 4/110 (3.6%) in group 2 (p<0.00001). Indeed, 53/57 patients (93%) practicing out-of-school physical activity prior to the lockdown had interrupted it for at least a month at V2, due to restrictive measures. In addition, patients of group B had not been attending school for a median time of 89.5 days (IQR: 71-106.7).

The rate of relapse was statistically significantly higher in group B (21/124, 16.9%, 95% C.I. 10.8-24.7%) in comparison to group A (8/126, 6.3%, 95% C.I. 2.8-12.1%) (p=0.009) (*table 2*). In fact, a new drug was started in 15.3% patients of group B compared to 6.3% of group A (p=0.022), while the proportion of patients undergone therapy tapering or discontinuation at V2 was only slightly lower in group B (15/81, 18.5% vs 25/90, 27.8%, p=0.153). More in details, with regard to flaring patients of group B, 16 patients started a NSAID, 4 a new cDMARD or bDMARD, while 3 underwent glucocorticoid joint injection(s) and 3/10 required an increased dosage of the ongoing DMARD therapy (*supplementary table S1*). When considering medication adherence, 11 out of 21 relapsing patients in group B were on medication at V2. None of these patients reported temporary therapeutic interruptions, compared to 5/70 inactive children (0% vs 7.1%, p>0.05). The face-to-face visit had been postponed for over a month in 33.3% of relapsed patients (7/21), the same as patients presenting ID (24/72, 33.3%, p=1). Data on out-of-school physical activity were available in 18 patients with JIA flare in group 2: 12 of them had interrupted physical activity due to

COVID-19 lockdown, 6 did not practice sport before COVID-19 pandemic. Of note, none of the flaring patients had neither suspected or confirmed COVID-19 diagnosis nor COVID-19 exposure and 5 of them had a negative SARS-CoV-2 serology in June 2020.

When comparing relapsed patients among the two groups, no differences in demographic and clinical features at V2 were found *(supplementary table S1)*. Notably, ankle arthritis was slightly more frequent in group B (38% vs 0%, p=0.066).

Discussion

To our knowledge, this study presented the largest pediatric JIA cohort in which the effects of COVID-19 lockdown on disease course were investigated. Our data showed that more JIA patients experienced a disease flare during home confinement due to SARS-CoV-2 pandemic compared to the same period of the previous year, supporting our hypothesis that containment measures during COVID-19 lockdown negatively impacted disease activity.

In contrast to the so far published data about the impact of COVID-19 pandemic on the course of inflammatory rheumatic diseases in adults (2-4), mostly based on patient-reported data, in our study, disease flare assessment required physician evaluation, thus increasing the strength of our findings. While Ciurea and colleagues found no detrimental impact of containment measures on the disease course in 666 patients with spondyloarthritis (SpA), rheumatoid arthritis or psoriatic arthritis (3), Roux et al observed a significant difference in the rate of severe disease flare in 512 SpA patients before and during home confinement (20% vs 49%) (2). So far, only one study reported an increase of JIA flares in a small cohort of 58 children during March–July 2020 (5), in agreement with our findings. The higher relapse rate reported by these two latter studies was mainly attributed to changes of treatment regimens due to concerns about COVID-19 (2, 5). Recently, a large survey did not reveal a decrease in therapy compliance during the first months of pandemic in about 4000 patients with rheumatic diseases (9). Accordingly, in our cohort, only one patient delayed the scheduled treatment due to apprehension of SARS-CoV-2 infection, down-sizing the possible impact of the pandemic outbreak on treatment adherence and thus on disease course. During lockdown, we remotely recommended patients to continue all therapies as usual, as suggested by the Paediatric Rheumatology European Association in March 2020 (10). This reassurance campaign might have limited the impact of COVID-19-related fears on therapeutic compliance. Yet, a role of decreased drug adherence on disease activity during lockdown could not be entirely excluded, as it was not measured through a validated tool.

During COVID-19 lockdown, children spent less time engaged in physical activity, with a parallel increase in sleeping and TV or video watching/playing time (11, 12). These lifestyle modifications may impact on daily life of patients with chronic diseases (13), and possibly contribute to a higher flare rate in JIA children. As expected, in our population the proportion of patients performing regular physical activity was significantly lower during COVID-19 pandemic compared to the previous year. In addition, our kids with JIA had not been attending school for about 3 months at the time of consultation. It is well-known that arthritis symptoms worsen in the morning or after prolonged rest (14) and that physical therapy may lead to pain reduction and increased range of motion in JIA patients (15). Indeed, along with medications, exercise is recommended as a therapeutic tool to children and adolescent with JIA in order to counteract the disease-related inflammation and improve clinical symptoms (16). Besides, it has been shown that peripheral blood lymphocytes of less active children present a proinflammatory profile, suggesting that physical activity may decrease systemic inflammatory responses (17). Therefore, the physical inactivity associated to home confinement could be a possible explanation for clinical worsening in our patients. On this basis, we believe that prescription of home-based exercise programs by a physical therapist should be promoted to implement JIA management in case of public lockdowns.

The temporary interruption of non-essential healthcare in person consultations during the "phase 1" of COVID-19 pandemic might have led to delays in patients' management, however the proportion of delayed face-to-face visits was the same in patients with or without arthritis relapse, suggesting that the limitations in the outpatient rheumatology medical service was not a main contributor to the JIA worsening in our cohort. As a matter of fact, outpatient in person visits were postponed only if parents reported no signs or symptoms consistent with JIA relapse at the telemedicine call. Even though recent data suggest that telemedicine alone may be insufficient to guide a treat-to-target strategy (18), the use of telehealth tools might have limited the impact of the partial closure of ambulatory services on disease management, according to other reports (19). From this point of view, the development of validated telemedicine models for JIA may be critical to guarantee an effective management of JIA in case of confinement measures and to monitor disease activity at home.

Our findings should be interpreted within the limitations of the study, which are mainly inherent to its observational and retrospective nature. Besides, our results reflect a single tertiary care center experience, so they may not be extended to other clinical settings. Since our study was not randomized and observational, we cannot exclude that patients in group B presented a more

aggressive disease than those in group A. Likewise, the slightly higher number of patients off-therapy in group B may represent a possible confounding factor in our analysis. Nevertheless, the comparison of the two cohorts showed homogeneity in regard to demographic and clinical features. Finally, since subtle signs of active arthritis might have been underrecognized and not reported at telemedicine, the relapse rate during lockdown could be even potentially higher than observed.

In conclusion, this study provides new evidence that COVID-19 lockdown was associated with a higher rate of relapse in JIA children, even in the absence of reduced drug adherence. This finding has considerable clinical implications, since restrictive measures are still occurring in several countries as the pandemic evolves. Our data highlight the need for implementing healthcare management of patients with JIA, including personalized at-home-exercise-programs, in case of new lockdowns.

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Figure legend

Figure 1. Diagram showing the composition of the patients' groups. Two groups of children affected by juvenile idiopathic arthritis were enrolled, all presenting with clinically inactive disease at enrollment (V1) and then evaluated (V2) before (group A) and during the first COVID-19 lockdown (group B). JIA: juvenile idiopathic arthritis; ID: inactive disease; sJIA: systemic juvenile idiopathic arthritis.

Table 1. Baseline characteristics of study patients.

	Group A N=126	**Group B N=124**	**p-value†**
Sex (female), n (%)	97 (77)	94 (75.8)	0.826
Median (IQR) age at JIA onset, yrs	4 (2.2-6.8)	4.2 (2-6.9)	0.71‡
Median (IQR) age at V1, yrs	10.9 (7.8-14.4)	10.9 (8-14.4)	0.933‡
Median (IQR) disease duration at V1, yrs	5.1 (3.2-8.6)	5.3 (2.7-8.5)	0.809‡
JIA Subtype, n (%)			
Oligoarticular	83 (65.8)	77 (62.1)	0.534
Polyarticular	35 (27.8)	41 (33.1)	0.364
Systemic	7 (5.6)	4 (3.2)	0.369
ERA	1 (0.8)	2 (1.6)	0.62§
ANA positivity, n (%)	58 (46)	52 (41.9)	0.514
History of uveitis, n (%)	28 (22.2)	26 (21)	0.81
Past JIA treatment, n (%)			
Intra-articular corticosteroid injections	45 (35.7)	40 (32.3)	0.564
Systemic corticosteroids	21 (16.7)	18 (14.5)	0.639
Methotrexate	54 (42.9)	65 (52.4)	0.13
Other conventional DMARDs	3 (2.4)	2 (1.6)	1§
Biological DMARDs	14 (11.1)	16 (12.9)	0.663
Ongoing JIA treatment at V1, n (%)			
NSAID	17 (13.5)	8 (6.5)	0.064
Systemic corticosteroids	0	1 (0.8)	0.496§
Methotrexate	59 (46.8)	46 (37.1)	0.119
Sulfasalazine	1 (0.8)	2 (1.6)	0.62§
Biological DMARDs	55 (43.7)	56 (45.2)	0.81
Etanercept	28 (22.2)	27 (21.8)	0.932
Adalimumab	15 (11.9)	14 (11.3)	0.879
Infliximab	2 (1.6)	3 (2.4)	0.682§
Tocilizumab	7 (5.6)	9 (7.3)	0.582
Canakinumab	0	1 (0.8)	0.496§

Abatacept	3 (2.4)	2 (1.6)	1§
Off-therapy	20 (15.9)	28 (22.6)	0.178
Out-of-school physical activity in the last month*	50/91 (54.9)	50/92 (54.3)	0.9

V1 frame: from September 1st, 2018 to March 9th, 2019 in group A; from September 1st, 2019 to March 9th, 2020 in group B.

IQR: interquartile range; JIA: juvenile idiopathic arthritis; ERA: Enthesitis-related arthritis; ANA: antinuclear antibody; DMARDs: disease modifying antirheumatic drugs; NSAID: Nonsteroidal anti-inflammatory drug.

† χ^2 test unless otherwise specified.

‡ Mann-Whitney U test.

§ Fisher's exact test.

*Data on sport activity outside school were available in 91 patients of group 1 and in 92 patients of group 2.

Table 2. Relapse rate and therapeutic regimens in group A and group B at V2.

	Group A N=126	**Group B N=124**	**p-value†**
Patients with JIA relapse at V2, n (%)	8 (6.3)	21 (16.9)	**0.009**
Ongoing JIA treatment at V2, n (%)			
NSAID	6 (4.8)	1 (0.8)	0.120§
Oral corticosteroids	0	0	
Methotrexate	45 (35.7)	35 (28.2)	0.204
Sulfasalazine	1 (0.8)	2 (1.6)	0.62§
Biological DMARDs	53 (42.1)	51 (41.1)	0.881
Etanercept	28 (22.2)	26 (21)	0.810
Adalimumab	14 (11.1)	10 (8.1)	0.414
Infliximab	1 (0.8)	3 (2.4)	0.368§
Tocilizumab	7 (5.6)	9 (7.3)	0.582
Canakinumab	0	1 (0.8)	0.496§
Abatacept	3 (2.4)	2 (1.6)	1§
Off-therapy	36 (28.6)	43 (34.7)	0.299
Therapeutic Decision at V2, n (%)			
Prescription of a new drug	8 (6.3)	19 (15.3)	**0.022**
Continuation of ongoing therapy	57/90 (63.3)	50/81 (61.7)	0.829
Dosage drug increase	3/90 (3.3)	4/81 (4.9)	0.709§
Drug tapering or one drug discontinuation*	25/90 (27.8)	15/81 (18.5)	0.153
Therapy withdrawal	3/90 (3.3)	4/81 (4.9)	0.709§
Out-of-school physical activity in the last month**	48/77 (62.3)	4/110 (3.6)	**<0.00001**

V2 frame: from March 10th, 2019 to June 30th, 2019 in group A; from March 10th, 2020 to June 30th, 2020 in group B.

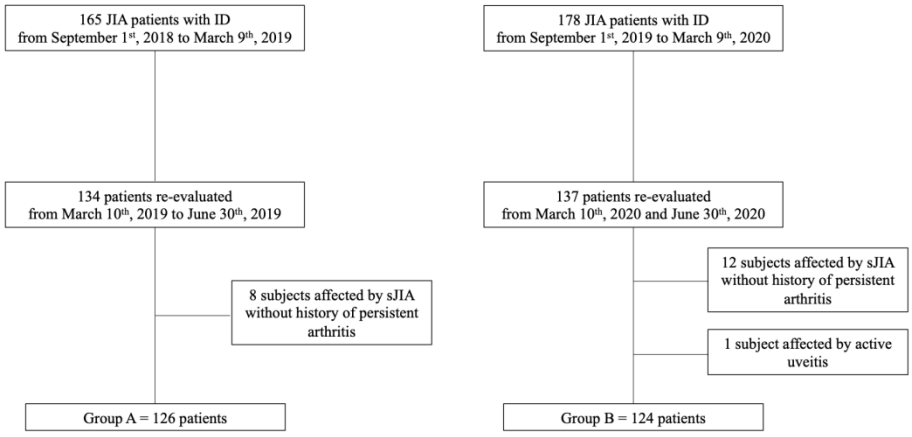
JIA: juvenile idiopathic arthritis; NSAID: Nonsteroidal anti-inflammatory drug; DMARDs: disease modifying antirheumatic drugs.

† χ^2 test unless otherwise specified.

§ Fisher's exact test.

*In case of combined medications regimens.

**Data on sport activity outside school were available in 77 patients of group 1 and in 110 patients of group 2.



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