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Influence of sex on disease severity in children with multisystem inflammatory syndrome and COVID-19 in Latin America

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Abstract. Data from adult studies show that COVID-19 is more severe in men than women. However, no data are available for the pediatric population. For this reason, we performed this study aiming to understand if sex influenced disease severity and outcomes in a large cohort of Latin-American children with COVID-19 and multisystem inflammatory syndrome (MIS-C). We found that a higher percentage of male children developed MIS-C (8.9% vs 5% in females) and died (1.2% and 0.4% in females), although on multivariate adjusted analyses the only statistically significant difference was found in need of hospitalization, with females less frequently admitted compared with boys (25.6% vs 35.4%). This data are preliminary and need further independent studies to better assess the role of sex.

Keywords. COVID-19, MIS-C, MIS, sex, gender, children.

Influenza del sesso sulla gravità della malattia nei bambini con sindrome infiammatoria multisistemica e COVID-19 in America Latina

Riassunto. I dati degli studi sugli adulti dimostrano che il COVID-19 si manifesta in modo più grave negli uomini che nelle donne; tuttavia, per la popolazione pediatrica non sono disponibili dati. Per questo motivo abbiamo condotto questo studio, con l'obiettivo di capire se il sesso ha influenzato la gravità e gli esiti della malattia in un'ampia coorte di bambini latino-americani con COVID-19 e sindrome infiammatoria multisistemica (MIS-C). Abbiamo notato che una più alta percentuale di bambini maschi ha sviluppato MIS-C (8,9% vs 5% nelle femmine) ed è morta (1,2%, vs 0,4% nelle femmine), sebbene nell'ambito di analisi multivariate aggiustate l'unica differenza statisticamente significativa sia stata identificata nella necessità di ospedalizzazione, con le femmine ricoverate con minor frequenza rispetto ai maschi (25,6% vs 35,4%). Questi dati sono preliminari e necessitano di ulteriori studi indipendenti per poter valutare meglio il ruolo del sesso.

Parole chiave. COVID-19, MIS-C, MIS, sesso, genere, bambini.

Introduction

Over a year after the description of the first cases of COVID-19 in China, several aspects of this pandemic are still unclear; among these, the different clinical impact of COVID-19 in females and males. Early data from China showed that men were more frequently infected by COVID-19 than women, and that men with underlying diseases (diabetes, hypertension and cardiovascular disease) developed a severe condition, with an increased mortality rate.[1] Similar findings were reported in Italy, and were subsequently confirmed in almost all other Countries.

Several hypotheses have been made to support these differences, although no definite conclusions have been reached yet. Disparities in sex-specific disease outcomes may be due to sex-specific steroids and the activity of X-linked genes, which modulate the innate and adaptive immune response to virus infection and affect the immune response.[2] Sex-related pre-existing comorbidities, such as hypertension, cardiovascular disease and diabetes, can play a role, since they are associated with severe outcomes, and are more frequent in men.[3] In addition, hormonal and genetic factors can affect the expression of ACE2 (the receptor of SARS-CoV-2),[4-6] microRNAs expressions and transcription,[7] and the vitamin D3 activity.[8]

However, whether or not such differences between sexes are present in the pediatric population has not yet been the subject of any analysis. Major pediatric papers mainly focus on age as a risk factors of disease severity but, to our knowledge, no sex-assessing sub-analyses have been described.[9-15] Since sex hormones or specific habits/conditions (alcohol, type-2 diabetes, and cardiovascular disease) are less pronounced in the pediatric population, in particular in infants and young children, such analysis can provide indirect evidence on the effect of hormones on COVID-19. Therefore, we performed

this study with the aim to understand whether sex affects disease severity and outcomes in a large cohort of Latin-American children with multisystem inflammatory syndrome (MISC) and COVID-19.

Materials and methods

Study design and participants

This study is part of an ongoing independent project – already presented elsewhere[12] – which assesses COVID-19 and MIS-C in Latin American children, with a previously published paper describing an initial group of 409 children with confirmed COVID-19.[14] For this study we performed a sub-analysis of a previously used dataset,[15] in order to evaluate the effect of sex on disease severity. The remaining variables are those previously described, and include age, gender, symptoms, imaging, underlying medical conditions, need for hospital and NICU/PICU admission, respiratory and cardiovascular support, other viral co-infections, drugs used to treat COVID-19, development of MIS-C and type of organ involvement, and outcome.

SARS-CoV-2 infection was confirmed through a positive PCR test with nasopharyngeal swab.

MIS-C was defined according to the CDC criteria (available at https://www.cdc.gov/mis-c/hcp/): an individual aged <21 years (we only subjects younger than 18) presenting with: i) fever; ii) laboratory evidence of inflammation; iii) evidence of clinically severe disease, requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); iv) no plausible alternative diagnoses; and v) positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposed to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

The study was reviewed and approved by the DOMINGO (CoviD in sOuth aMerIcaN children-study GrOup) core group and approved by the Ethics Committee of the coordinating center and by each participating center (Mexico: COMINVETICA-30072020-CEI01001201 60207; Colombia: PE-CEI-FT-06; Peru: No. 42-IETSI-ESSALUD-2020; Costa Rica: CEC-HNN-243-2020). The study was conducted in accordance with the Declaration of Helsinki and its amendments. No personal or identifiable data were collected during the study.

Statistical analysis

Summary statistics were presented as counts and percentages. The association between female sex and COVID-19 clinical outcomes was preliminarily evaluated with crude odds ratios (ORs) and 95% confidence intervals (CIs). A confounding adjustment was performed using a propensity score approach based on inverse-probability weighting. More specifically, we considered the following covariates, potentially related with the outcomes and unbalanced across males and females: age, pre-existing medical conditions, immunosuppressant at the time of diagnosis, primary or secondary immunodeficiency, chemotherapy over the last 6 months, pyrexia (≥38.0 °C/≥100.4 °F), days between the onset of symptom and the diagnosis, administration of systemic corticosteroids, intravenous immunoglobulin therapy, lower respiratory tract infection, and diagnosis of MIS-C. Clustered standard errors were used to account for the multicenter design of the study. All data were analyzed using the Stata 15 software (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC). The significance level was set at 5%, and all tests were 2-sided.

Results

The characteristics of the 990 patients enrolled in the study – both overall and by sex – are summarized in Table 1. Children were enrolled in Peru (383), Costa Rica (299), Argentina (253), Colombia (43), and Mexico (12). Among the 484 females, 313 (64.7%) had fever, 223 (46.1%) signs of upper respiratory tract infection, 143 (29.5%) diarrhea and/or vomiting, 86 (17.8%) signs of lower respiratory tract infection, and 52 (10.7%) headache; 39 (8.1%) had chest X-ray abnormalities, 124 (25.6%) were hospitalized, 20 (4.1%) were admitted to ICUs, 49 (10.1%) received respiratory support, and 2 (0.4%) died; 24 (5%) were diagnosed with MIS-C. Among the 506 males, 53 (10.5%) had chest X-ray abnormalities, 179 (35.4%) were hospitalized, 27 (5.3%) were admitted to ICUs, 69 (13.6%) received respiratory support, and 6 (1.2%) died; 45 (8.9%) were diagnosed with MIS-C. Systemic steroids (38, 7.9%) and intravenous immunoglobulins (21, 4.3%) were used in similar proportions of females and males.

Table 2 shows the results of the crude and adjusted analyses, demonstrating the association between sex and clinical outcomes. Following an adjustment obtained with a weighting approach based on propensity scores, the only significant outcome was the access to the hospital: girls were admitted less frequently than boys (OR = 0.82, p <0.001).

Discussion

In this study, we aimed to assess the impact of sex on disease severity in a large cohort of Latin American children with COVID-19 and MIS. We found that a higher percentage of male children developed MIS (8.9% vs 5%

Table 1. Characteristics of the study sample, overall and by sex

Characteristics	All (n = 990)		Males (n = 506)		Females (n = 484)	
	No.	%	No.	%	No.	%
Age group						
0 y	202	20.4	99	19.6	103	21.3
1-2 y	229	23.1	123	24.3	106	21.9
3-5 y	144	14.5	80	15.8	64	13.2
6-11 y	247	24.9	137	27.1	110	22.7
12-17 y	168	17.0	67	13.2	101	20.9
COVID-19 confirmed by real-time PCR	639	64.5	345	68.2	294	60.7
Positive SARS-CoV-2 IgG	352	35.6	159	31.4	193	39.9
Delay between onset and diagnosis						
0-1 d	437	44.1	234	46.2	203	41.9
2-7 d	460	46.5	236	46.6	224	46.3
>7 d	93	9.4	36	7.1	57	11.8
Likely index case						
Parent	281	28.4	149	29.4	132	27.3
Sibling	14	1.4	6	1.2	8	1.7
Other	120	12.1	63	12.5	57	11.8
Unknown	575	58.1	288	56.9	287	59.3
Medical history						
Known history of BCG vaccine	740	74.7	402	79.4	338	69.8
Pre-existing medical conditions	128	12.9	76	15.0	52	10.7
Immunosuppressants at diagnosis	11	1.1	9	1.8	2	0.4
Primary or secondary immunodeficiency	8	0.8	6	1.2	2	0.4
Chemotherapy over the last 6 months	8	0.8	5	1.0	3	0.6
Symptoms						
Pyrexia (≥38.0 °C/≥100.4 °F)	677	68.4	364	71.9	313	64.7
Upper respiratory tract infection	466	47.1	243	48.0	223	46.1
Diarrhea and/or vomiting	301	30.4	158	31.2	143	29.5
Lower respiratory tract infection	215	21.7	129	25.5	86	17.8
Headache	104	10.5	52	10.3	52	10.7
Administration of inotropes	29	2.9	19	3.8	10	2.1
Co-infections in respiratory samples(s)	14	1.4	11	2.2	3	0.6

Continues

Table 1. *Continued*

Characteristics	All (n = 990)		Males (n = 506)		Females (n = 484)	
	No.	%	No.	%	No.	%
Drug administration						
Systemic corticosteroids	90	9.1	52	10.3	38	7.9
Intravenous immunoglobulin (IVIG)	60	6.1	39	7.7	21	4.3
Direct acting antiviral drugs	10	1.0	6	1.2	4	0.8
Hydroxychloroquine	9	0.9	5	1.0	4	0.8
MIS-C diagnosis	69	7.0	45	8.9	24	5.0
Country						
Peru	383	38.7	178	35.2	205	42.4
Costa Rica	299	30.2	169	33.4	130	26.9
Argentina	253	25.6	127	25.1	126	26.0
Colombia	43	4.3	25	4.9	18	3.7
Mexico	12	1.2	7	1.4	5	1.0

COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IgG, immunoglobulin G; BCG, bacillus Calmette-Guérin; MIS-C, Children with multisystem inflammatory syndrome.

Table 2. Crude and adjusted association between female sex and COVID-19 clinical outcomes, expressed as odds ratios (OR) and 95% confidence interval (CI)

Outcome	No. (%)	Crude analysis			Adjusted analysis*		
		OR	95% CI	P-value	OR	95% CI	P-value
Chest X-ray abnormalities†	92 (9.3)	0.75	0.58-0.96	0.022	1.09	0.86-1.36	0.480
Hospital admission	303 (30.6)	0.63	0.55-0.72	<0.001	0.82	0.78-0.86	<0.001
ICU admission	47 (4.7)	0.76	0.64-0.92	0.004	1.15	0.94-1.40	0.173
Respiratory support‡	118 (11.9)	0.71	0.58-0.88	0.001	1.08	0.87-1.34	0.487
Death	8 (0.8)	0.34	0.07-1.65	0.183	0.43	0.09-2.10	0.297

*Confounding adjustment obtained with a weighting approach based on propensity scores.
†Pneumonia and/or acute respiratory distress syndrome.
‡Oxygen support, mechanical ventilation and/or continuous positive airway pressure therapy.
ICU, Intensive Care Unit.

in females) and died (1.2% vs 0.4% in females), although – upon multivariate adjusted analyses – the only statistically significant difference was found to be the need for hospitalization, with females less frequently admitted than males (25.6% vs 35.4%). Overall, this preliminary data highlights the fact that females can experience a milder disease compared with boys, as suggested in adults. In other reports,[6] females were more frequently affected by hyposmia or anosmia and taste dysfunction compared with males; unfortunately, we did not assess these parameters in this study. In our cohort, children had no comorbidities such as hypertension, obesity or type-2 diabetes, therefore these behavioral factors, traditionally more frequent in males, could not have contributed to the described differences. Also, considering that sex hormones may have less impact in children, different microRNAs expressions due to sex hormones would not be involved as well.

An explanation of the disparity in sex-specific disease outcomes can be found in the activity of X-linked genes,

as previously suggested,[6] which modulate the innate and adaptive immune response to virus infection and affect the immune response. In addition, the male predominance in the COVID-19 pandemic could be partially explained by the sex-specific expressions of TMPRSS2.[6]

The activity and expression of the human angiotensin-converting enzyme 2 (ACE2) – the functional receptor for the severe acute respiratory syndrome coronavirus (SARS-CoV) – can also explain some differences. Age-related differences have been already suggested in a review.[16] In rodents, pulmonary ACE2 expression is developmentally regulated, being at its highest at an early age and at its lowest when mice reach adulthood. Studies in rat lungs confirmed that ACE2 is predominantly expressed in the alveolar and bronchiolar epithelium, with the ACE2 expression dramatically reduced with age in both genders, with old male rats showing a more pronounced decrease.[16] Also, hormonal and genetic factors could lead to ACE2 over-expression in the female sex. Gagliardi et al.[6] reported that the SARS-CoV infection induces ACE2 down-regulation through the binding of the viral Spike protein to ACE2, thus reducing ACE2 expression in the lung, and triggering acute respiratory failure.[17]

Vitamin D has also received attention in the context of the immune pathogenesis of COVID-19[17] and Pagano et al. hypothesized that the synergy between vitamin D3 and estrogen could affect the sex differences in the outcome of COVID-19 patients.[18,19] However, no rigorous data is yet available on these issues and, in our data series, vitamin D levels have not been reported.

Sex may play a major role in the severity and persistence of the symptoms after the first diagnosis of acute COVID-19. In adults, long COVID has been described, and it seems more frequent in women.[20-21] International experts highlighted the possibility of this disease in childhood as well, and recent reports seem to confirm that long COVID may affect children too.[22-24] Since autoimmunity has been suggested as a potential pathogenic trigger – and considering the higher frequency of autoimmune disorders in children – the role of sex in long COVID, including in children, is a priority research topic for the next months.

Our study has limitations to be considered. First, it was not initially developed to specifically understand how sex could affect disease severity, therefore the variables included – as well as the study power – were not tailored to this subject. Also, blood tests, hormones and vitamin D were not tested, and therefore not analyzed. Lastly, there isn't a control group of adult patients from the same area to compare sex differences in the various age groups. However, this study is the first to specifically assess the role of sex in children with COVID-19 and MIS.

In conclusion, we found a slightly more severe course of COVID-19 and MIS occurring in males than in females in our cohort of Latin American children. This data is preliminary, and further independent studies are needed to better assess the role of sex. In light of the growing evidence on long COVID in children, it is important to start including sex as an important potential variable of symptoms severity or persistence in COVID-19 children.

Key messages

- Gender differences in pediatric COVID-19 have not yet been assessed.
- In our cohort, a higher – albeit not significant – percentage of male children developed MIS-C (8.9% vs 5% in females) and died (1.2% vs 0.4% in females).
- Males presented a statistically significantly higher admission rate.
- The role of sex hormones in pediatric COVID-19 is still unknown.
- More studies are needed to better understand how gender affects disease severity in children of different age groups.

References

1. Ambrosino I, Barbagelata E, Ortona E, et al. Gender differences in patients with COVID-19: a narrative review. Monaldi Arch Chest Dis. 2020;90(2).
2. Ghosh S, Klein RS. Sex drives dimorphic immune responses to viral infections. J. Immunol. 2017;198(5):1782-90.
3. Vardavas CI, Nikitara K. COVID-19 and smoking: a systematic review of the evidence. Tob Induc Dis. 2020;18:20.
4. Bukowska A, Spiller L, Wolke C, et al. Protective regulation of the ACE2/ACE gene expression by estrogen in human atrial tissue from elderly men. Exp Biol Med (Maywood). 2017;242(14):1412-23.
5. Tukiainen T, Villani A-C, Yen A, et al. Landscape of X chromosome inactivation across human tissues. Nature. 2017;550(7675):244-8.
6. Gagliardi MC, Tieri P, Ortona E, Ruggieri A. ACE2 expression and sex disparity in COVID-19. Cell Death Discov. 2020;6:37.
7. Pontecorvi G, Bellenghi M, Ortona E, Carè A. MicroRNAs as new possible actors in gender disparities of Covid-19 pandemic. Acta Physiol (Oxf). 2020;230(1):e13538.
8. Pagano MT, Peruzzu D, Ruggieri A, et al. Vitamin D and sex differences in COVID-19. Front Endocrinol (Lausanne). 2020;11:567824.
9. Viner RM, Mytton OT, Bonell C, et al. Susceptibility to SARS-CoV-2 infection among children and adolescents compared with adults: a systematic review and meta-analysis. JAMA Pediatr. 2021;175(2):143-56.
10. Götzinger F, Santiago-García B, Noguera-Julián A, et al. COVID-19 in children and adolescents in Europe: a mul-

tinational, multicentre cohort study. Lancet Child Adolesc Health. 2020;4(9):653-61.
11. Parri N, Lenge M, Cantoni B, et al. COVID-19 in 17 Italian pediatric emergency departments. Pediatrics. 2020;146(6): e20201235.
12. Parri N, Magistà AM, Marchetti F, et al. Characteristic of COVID-19 infection in pediatric patients: early findings from two Italian pediatric research networks. Eur J Pediatr. 2020;179(8):1315-23.
13. Antúnez-Montes OY, Escamilla MI, Figueroa-Uribe AF, et al. COVID-19 in South American children: a call for action. Pediatr Infect Dis J. 2020;39(10):e332-e334.
14. Antúnez-Montes OY, Escamilla MI, Figueroa-Uribe AF, et al. COVID-19 and multisystem inflammatory syndrome in Latin American children: a multinational study. Pediatr Infect Dis J. 2020;40(1):e1-e6.
15. Yock-Corrales A, Lenzi J, Ulloa-Gutiérrez R, et al. Antibiotic prescriptions in children with COVID-19 and multisystem inflammatory syndrome: a multinational experience in 990 cases from Latin America. Acta Paediatr [Internet]. 2021. Available from: https://onlinelibrary.wiley.com/doi/10.1111/apa.15847?af=R.
16. Buonsenso D, Sali M, Pata D, et al. Children and COVID-19: microbiological and immunological insights. Pediatr Pulmonol. 2020;55(10):2547-55.
17. Hanff TC, Harhay MO, Brown TS, et al. Is there an association between COVID-19 mortality and the renin-angiotensin system? A call for epidemiologic investigations. Clin Infect Dis. 2020;71(15):870-4.
18. Turrubiates-Hernández FJ, Sánchez-Zuno GA, González-Estevez G, et al. Potential immunomodulatory effects of vitamin D in the prevention of severe coronavirus disease 2019: an ally for Latin America (Review). Int J Mol Med. 2021;47(4):32.
19. Pagano MT, Peruzzu D, Ruggieri A, et al. Vitamin D and sex differences in COVID-19. Front Endocrinol (Lausanne). 2020;11:567824.
20. Carfì A, Bernabei R, Landi F, Gemelli against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. JAMA. 2020;324(6):603-5.
21. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397(10270):220-32.
22. Munblit D, Buonsenso D, Dunn Galvin A, et al. The risk of overlooking children during the COVID-19 pandemic: paediatric long-COVID may be a ticking time bomb. Lancet Child Adolesc Health. 2021; accepted.
23. Buonsenso D, Munblit D, De Rose C, et al. Preliminary evidence on long COVID in children. Acta Paediatr. [Internet]. 2021. Available from: https://onlinelibrary.wiley.com/doi/10.1111/apa.15870.
24. Buonsenso D, Espuny Pujol F, Munblit D, et al. Clinical characteristics, activity levels and mental health problems in children with long COVID: a survey of 510 children. Preprints [Internet]. 2021. Available from: https://www.preprints.org/manuscript/202103.0271/v1.

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