Study of Prevalence and Characteristics of Long Covid in Spanish Children

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Research Article

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Abstract

Objectives

Prolonged symptoms after acute COVID-19 have been described in the pediatric population. Our objective was to know the prevalence of prolonged symptoms in children with confirmed SARS-CoV-2 infection, and to describe their clinical characteristics and possible risk factors.

Patients & methods

Multicentre retrospective study carried by telephone questionnaire of all children under 18 years old diagnosed of symptomatic COVID-19, both hospitalized and outpatient attended in three hospitals in Spain between March and December 2020. Long-COVID was defined as the presence of symptoms longer than 12 weeks. A control group of children attended by other causes was also contacted and compared.

Results

451 children met criteria and agreed to participate; 370/451 (82%) presented mild outpatient infection, and 23 required admission in PICU (5.1%). The mean age was 5.9 years old (SD 5.3). A control group of 98 children was included.

In 66 cases (14.6%) at least one symptom lasted longer than 12 weeks. Insomnia, concentration problems, apathy or sadness and anxiety were the longest (median >90 days). Age above 5 years (48/66; 72.7%, OR: 3, CI 95% (1.8-5)); admission (OR 3.9 CI 95% (2.2-6.8)), the need for PICU (OR 4.3 CI 95% (1.8-10.4)), and to have a relative with prolonged symptoms (OR 2.8 CI 95% (1.5-5.2)) were significantly associated with Long-COVID. When comparing with controls age above 5 years old, myalgia, asthenia, and loss of appetite were significantly associated with Long-COVID.

Conclusions

Our study shows that children also suffer prolonged symptoms after COVID-19 infection, and require specific attention.

Introduction

SARS-CoV-2 infection in children is relatively mild, or at least clearly less severe than in adults, being hospitalization less frequent. However, there is a small percent of serious cases, both in the acute phase (mainly pneumonia) and lately, as the multisystemic inflammatory syndrome (MIS-C), many of them requiring admission in the pediatric intensive care unit (PICU).

The presence of prolonged symptoms lasting more than 12 weeks after the acute infection has been described in pediatric population in a similar way than in adult population. It has been called Long-COVID or persistent COVID, and the prevalence in childhood and its characteristics are poorly described, having been detected in some series in up to 20% of cases, while in others the frequency does not reach 2%, possibly due to the methodology used^{1,2,3,4}. The UK Office for National Statistics estimates that 9.8% of children between 2 and 11 years old and 13% of children between 12 and 16 years old have symptoms 5 weeks after the infection. After 12 weeks, 7.4% of children between 2 and 11 years old, and 8.2% of children between 12 and 16 years old continue to have persistent symptoms⁵.

There is not a universally accepted definition for this entity yet, although the most accepted one considers a pediatric patient with persistent COVID-19 as a minor under 18 years old of age diagnosed with COVID-19 (with microbiological confirmation) who, after 12 weeks of infection, continues presenting symptoms, without recovering their previous health status⁶.

In children, as in adults, persistent COVID-19 translates into a decrease in the quality of life, which in many cases even implies not being able to go to school. It is considered that frequently these symptoms have gone unnoticed and were not initially attributed to SARS-CoV-2 infection, and it is only recently that awareness of this problem has begun^{7,8}. It is necessary to carry out an early diagnosis and an adequate follow-up. In children, this care is especially necessary since these patients are in a stage of emotional, physical and cognitive development⁹.

Our main objective was to know the prevalence of prolonged symptoms or Long-COVID in children with a confirmed SARS-CoV-2 infection in Spain, to describe the clinical characteristics of Long-COVID and identify possible risk factors in our population.

Patients And Methods

This is a multicentre retrospective study carried out at three hospitals in Madrid (La Paz University Hospital, Niño Jesús University Hospital and Severo Ochoa University Hospital), by telephone follow-up of all children diagnosed of symptomatic COVID-19 infection, both hospitalized and outpatient, and attended in any of the three hospitals, between March and December 2020. A prolonged COVID symptom questionnaire specifically designed was conducted by telephone call between August and September 2021. The study was approved by the Ethics Committee of La Paz Hospital (PI-4212) and the other centers. The Ethics Committee approved obtaining consent by telephone from the parents, incorporating the data into the patient's medical history. The questionnaire was performed by attending physicians.

Inclusion criteria were children under 18 years old with a confirmed diagnosis of SARS-CoV-2 infection by PCR, antigen test or serology between March and December 2020 with any symptoms related to SARS-CoV-2 infection, and whose parents or legal guardians agreed to participate in the telephone follow-up. Exclusion criteria were asymptomatic SARS-CoV-2 infection.

Persistent COVID was defined as the presence of symptoms for a period longer than 12 weeks.

A control group of children without a history of COVID-19 treated in the three centers during the same period, both in the emergency room without admission, and hospitalized, were randomly selected. The same symptom questionnaire starting from the time of their visit to the hospital was carried out by telephone by the same physicians.

Statistical analysis

The following variables were collected in a specific questionnaire: a) Demographic: date of birth, sex, date of diagnosis, symptoms onset date; b) Related to acute SARS-CoV-2 infection: diagnostic method, clinical diagnosis, need for admission, need for admission to the PICU; c) Persistence of symptoms: symptoms and duration, need for medical assistance, type of assistance and studies carried out and d) other data as comorbidities, result of serology, another affected relative, and patients' feeling of not have been understood due to their symptoms (feeling of misunderstanding). Some symptoms such as anosmia, ageusia, or symptoms as sadness, apathy or anxiety were only assessable in older children (generally older than 5 years). The main variable was the presence of at least one symptom lasting more than 12 weeks.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), Version 21.0. Values were expressed as percentages for discrete variables, and as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables. The demographic, clinical and evolutionary characteristics were compared using the Mann-Whitney U test, and Fisher's exact test, as appropriate. A value of $P < 0.05$ was considered statistically significant.

Results

A total of 668 children under 18 years old of age met the inclusion criteria and 451 (67.5%) could be contacted and agreed to participate, being the study population. A total of 248/451 (55%) were males and 370/451 (82%) presented mild infection with outpatient management during the COVID-19 infection, whereas 23 of them required PICU admission (5.1%). The mean age of the cohort was 5.9 years (SD 5.3), with 239/451 (53%) under 5 years old. Up to 60 children had any comorbidity (13.3%), with respiratory chronic diseases or asthma and immunosuppression as most frequent. The most common diagnosis related with COVID-19 was febrile syndrome 180/451 (39.9%) followed by upper respiratory tract infection (URTI) 148/451 (32.8%) and lower respiratory tract infection (LRTI), including pneumonia, bronchiolitis and asthma crisis in 46/451 (9.4%) of cases. MIS-C was present in 13 patients (2.9%).

The symptoms analysed and their duration are shown in Table 1. Most children with persistent symptoms were older than 5 years (48/66; 72.7%, OR: 3, CI 95% (1.8-5)). Some symptoms were not evaluable in infants and young children (as anosmia, ageusia, apathy or feeling sad, anxiety or concentration problems). Fever, rhinorrhoea and cough were the most frequent symptoms, generally with short duration (median less than 5 days). Some symptoms persisted for more than 4 weeks in 83 children (18.4%). In 66 cases (14.6%) at least one symptom, that parents associated with SARS-CoV-2 infection, lasted longer than 12 weeks. Only 37 children (8.2%) had two or more persistent symptoms (median 2, IQR 1-3). Insomnia, concentration problems, apathy or sadness and anxiety were the longest ones, all of them above a median of 90 days. A variety of prolonged symptoms were described in 6% of children, among which hair loss, memory loss or skin lesions stood out.

Table 1
Symptoms and duration in the total cohort of children with COVID-19.

	N (%)	Days of duration; median (IQR)
Rhinorrhea	212 / 451 (47%)	3 (3-5)
Fever	357/ 451 (79.1%)	3 (2-4)
Cough	218/ 451 (48.3%)	4 (3-7)
Difficulty breathing	93/451 (20.6%)	4 (2.5-7)
Diarrhoea	133/451 (29.5%)	3 (2-5)
Vomits	101/451 (22.4%)	2 (1-3)
Abdominal pain	90/433 (20.7%)	3 (2-7)
Headache	101/265 (38.1%)	4 (3-10)
Loss of appetite	204/451 (45.2%)	5 (3-10)
Anosmia/ ageusia	33/220 (15%)	15 (7.5-60)
Myalgia	81/430 (18.8%)	5 (3-15)
Asthenia	155/337 (46%)	8 (4-30)
Insomnia	21/326 (6.4%)	300 (52-422)
Concentration problems	22/211 (10.4%)	90 (15-253)
Apathy, feeling sad	19/225 (8.4%)	145 (97.5-298.7)
Anxiety	24/225 (10.6%)	205 (97.5- 361.2)
Palpitations / tachycardia	7/225 (3.1%)	15 (3.2- 30)
Dizziness	15/225 (6.6%)	4 (2-60)
Others*	30/451 (6.6%)	302.5 (112.5-272.5)
N: number of cases; IQR: interquartile range		
*Other symptoms include mainly loss of hear; memory loss, constipation, and skin lesions.		

Children with persistent symptoms required complementary tests in 44% of cases (29/66), with chest X-ray (12/66; 18%) and blood test (23/66; 35%) the most frequents, but with a variety of other tests, including spirometry and ultrasound. Almost half of patients (28/66; 42.4%) needed specialized care and not just primary care.

The clinical characteristics of the children with persistent symptoms were compared with the rest of patients and are shown in Table 2. Admission (OR 3,9) and its duration, need for PICU (OR 4.3), more severe diagnoses (as pneumoniae or MIS-C) and the existence of a relative with prolonged symptoms (OR 2.8) were significantly associated with prolonged symptoms. However, comorbidities were not associated with persistent symptoms. Presenting dyspnoea, diarrhoea and abdominal pain, even if they were short-lived, were associated with persistent symptoms. When present, symptoms such as headache, anosmia/ageusia, myalgia, asthenia, concentration problems, insomnia, apathy or feeling sad, anxiety, palpitations/tachycardia and dizziness, were significantly associated with Long COVID.

Table 2
Comparison between children with persistent symptoms >12 weeks (Long-COVID) and the remaining cohort.

	Long-COVID N=66/451 (14.6%)	No persistent symptoms N= 385/451	
Male gender	40 (60%)	208 (54%)	p=0.35
Admission	26 (39.4%)	55 (14.3%)	OR: 3.9, CI 95% (2.2-6.8)
Days of admission	5.8 (SD 3.1)	4.4 (SD 2.6)	p=0.047
PICU admission	10 (15.2%)	13 (3.9%)	OR: 4.3, CI 95% (1.8-10.4)
COVID-19 diagnosis	UTRI 24 (36%)	124 (32%)	p=0.001
	Febrile syndrome 16 (24%)	164 (42%)	
	Pneumonia 11 (16.7%)	15 (3.9%)	
	LRTI 1 (1,5%)	19 (5%)	
	Gastroenteritis 5 (7.6%)	31 (8%)	
	MIS-C 6 (9%)	7 (1.8%)	
Comorbidity	11 (16.7%)	49 (12.7%)	p=0.43
Another family member with Long COVID	20 (36.4%)	60 (16.9%)	OR: 2.8, CI 95% (1.5-5.2)
Rhinorrhoea	26 (39.4%)	186 (48.3%)	p=0.185
Fever	53 (80.3%)	306 (79.5%)	p= 0.345
Cough	39 (59%)	177 (46%)	p=0.051
Dyspnoea	32 (48.5%)	60 (15.6%)	OR: 5.09, CI 95% (2.9-8.8)
Diarrhoea	29 (44%)	104 (27%)	OR: 2.1, CI 95% (1.2-3.6)
Vomits	21 (31.8%)	80 (20.8%)	p=0.130
Abdominal pain	23/62 (37%)	67/361 (18%)	OR: 2.6, CI 95% (1.5-4.7)
Loss of appetite	36 (54.5%)	168 (43.6%)	p=0.100
Headache	32/55 (58.2%)	69/310 (32.9%)	OR: 2.8, CI 95% (1.5-5.2)
Anosmia/ageusia	17/54 (31.5)	16/166 (9.6%)	OR: 4.3, CI 5% (1.9-9.3)
Myalgia	27/61 (44.3%)	54/319 (15%)	OR: 4.4, CI 95% (2.5-8)
Asthenia	44/60 (73.3%)	111/277 (40%)	OR: 4.1, CI 95%(2.2-7.6)
Concentration problems	16/52 (30.8%)	6/159 (3.8%)	OR: 11.3, CI 95% (4.1-30.9)
Insomnia	14/60 (23.3%)	7/266 (2.6%)	OR: 11.2, CI 95% (4.3-24.4)
Apathy, sad feeling	17/54 (31.5%)	2/171 (1.2%)	OR: 28.8, CI 95% (8.5-178.3)
Anxiety	22/55 (40%)	2/170 (1.2%)	OR: 56 CI 95% (12.5-249.6)
Palpitations / tachycardia	6/54 (11%)	1/170 (0,6%)	OR: 21.1, CI 95% (2.4-179.7)
Dizziness	8/54 (14.8%)	7/171 (4.1%)	OR: 4.07 CI 95% (1.4-11.8)
>5 years old	48 (72.7%)	164 (42.6%)	OR: 3, CI 95% (1.8-5)
Age (years)	8.7 (SD 5.3)	5.4 (SD 5.2)	p=0.001
PICU: Pediatric intensive care unit. UTRI: Upper tract respiratory infection, LRTI: lower tract respiratory infection, OR: odds ratio, CI: confidence interval, SD: standard deviation.			

As persistent symptoms were more common in children older than 5 years (212 (47%)), these two groups, younger and older than 5 years, were compared. Any symptom lasting more than 4 weeks was observed in 26.9% (57/212) of children > 5 years compared to 10.9% (26/239) in < 5 years, p=0.001. Symptoms lasting more than 12 weeks were observed in 48/212 (22.6%) children > 5 years vs. 18/239 (7.5%) in the youngest group, p=0.001. Although the diagnoses

were slightly different (more MIS-C and pneumonia in > 5 years), the percentage of hospitalization and PICU admission were not significantly different. The prevalence of symptoms in the two groups and their duration is shown in Figure 1.

Control group

A total of 150 children were selected as control group between patients attended at emergency room, hospitalized or as outpatients in the same period. The children were chosen from among those with endocrinological, trauma or surgical pathology. Of them 98 (65.3%) met the criteria (have not had a SARS-CoV-2 infection) and agreed to participate; being 79 (80.6%) outpatients and 19 (19.4%) hospitalized. Two of them were admitted to PICU (one diabetic debut and one acute encephalitis). Fifty six (57.1%) were male, and mean age was 7.8 years (SD 4.2), with 28 (28.6%) under 5 years old. Clinical characteristics comparing control group with COVID-19 patients are shown in Table 3. It is noteworthy that up to 20 children (20.4%) reported symptoms lasting 4 weeks and 19 (19.4%) persistent symptoms for more than 12 weeks, and these percentages were not significantly different from children with COVID-19. Given that the children in the control group were significantly older, the percentages of persistent symptoms in children older than 5 years were analyzed in both groups and no significant differences were obtained between cases and controls (Table 3). However, both, symptoms over 4 weeks and persistent symptoms over 12 weeks were significantly associated with being over 5 years of age. Thus, for symptoms of more than 4 weeks (11.3% in <5 years vs 25.8% in > 5 years) an OR = 2.7, CI 95% (1.7-4.3) was observed. In the case of persistent symptoms of more than 12 weeks, they were also significantly more frequent in older children (8.3% in <5 years vs 22.3% in > 5 years) with an OR = 3.1, CI 95% (1.8-5.3).

Table 3
Comparison between children with COVID-19 and control group.

	COVID-19 N=451	Control group N= 98	
Male gender	248 (55%)	56 (57%)	p=0.761
Admission	81 (17.9%)	19 (19.4%)	p=0.690
PICU admission	23 (5.1%)	2 (2%)	p=0.131
Comorbidity	62 (13.7%)	14 (14.3%)	p=0.845
Primary care need assistance	95 (21.06%)	8 (8.2%)	p=0.004 OR: 2.5, CI 95% (1.2-5.1)
Need specialized assistance	51 (11.3%)	16 (16.3%)	p= 0.152
Any symptom more than 4 weeks	83 (18.4%)	29 (20.4%)	p=0.597
Persistent symptoms more than 12 weeks	66 (14.6%)	19 (19.4%)	p=0.214
>5 years old	239 (53%)	70 (71.4%)	p=0.001
Age (years)	5.9 (SD 5.3)	7.8 (SD 4.2)	p=0.001
Any symptom more than 4 weeks > 5 years old	58/239 (24%)	15/70 (21.4%)	p=0.386
Persistent symptoms more than 12 weeks > 5 years old	29/239 (20.5%)	14/70 (20%)	p=0.663
PICU: Pediatric intensive care unit, OR: odds ratio, CI: confidence interval, SD: standard deviation.			

To characterize the persistence of symptoms in children with COVID-19 (Long COVID), this specific group was compared in cases and controls older than 5 years (Table 4). The Long COVID group required significantly more complementary tests (p=0.02) and a trend of more assistance from their primary care paediatrician (p=0.056). Loss of appetite (p=0.005), myalgias (p=0.026), and asthenia (p=0.001) were significantly associated with Long COVID, but the rest of the symptoms had a similar frequency between cases and controls. In children under 5 years of age, only loss of appetite (47% vs 0) was more frequent in cases with a tendency to significance (p = 0.076).

Table 4
Comparison between children > 5 years old with persistent symptoms more than 12 weeks in COVID-19 and control group.

	COVID-19 N=49	Control group N= 14	
Male gender	28 (57.1%)	7 (50%)	p=0.635
Admission	20 (40.8%)	5 (35.7%)	p=0.731
PICU admission	20 (20.4%)	0	p=0.064
Comorbidity	9 (18.4%)	3 (21.4%)	p=0.797
Complementary test after acute episode	26 (53.1%)	1 (11.1%)	p=0.020 OR control group 0.77, CI 95% (0.61-0.96)
Primary care need assistance	28 (57.1%)	4 (28.6%)	p=0.056
Abdominal pain	21 (42.9%)	3 (33.38%)	p=0.594
Loss of appetite	28 (57.1%)	2 (14.3%)	p=0.005 OR: 5.4, CI 95% (1.3-22.4).
Headache	31 (63.3%)	5 (35.7%)	p=0.063
Myalgia	27 (55.1%)	1 (11.1%)	p=0.026 OR: 10.4, CI 95% (1.4-74)
Asthenia	39 (79.6%)	3 (21.4%)	p=0.001 OR: 7.3, CI 95% (2.2-23.4)
Concentration problems	15 (31.3%)	2 (14.3%)	p=0.211
Insomnia	11 (22.4%)	4 (28.6%)	p=0.635
Apathy, feeling sad	15 (31.3%)	2 (14.3%)	p=0.211
Anxiety	22 (44.9%)	8 (57.1%)	p=0.418
Palpitations / tachycardia	6 (12.5%)	1 (7.1%)	p=0.577
Dizziness	8 (16.3%)	1 (7.1%)	p=0.386
Other symptoms	16 (34.8%)	2 (14.3%)	p=0.143
PICU: Pediatric intensive care unit. OR: odds ratio, CI: confidence interval, SD: standard deviation.			

Discussion

Persistent COVID or long-term COVID in children is still a subject under study and debate, with insufficient data. In our multicenter study in Spain, with 451 children with confirmed symptomatic SARS-CoV-2 infection, we found 18.4% of cases with symptoms that lasted more than 4 weeks and 14.6% more than 12, which represent quite high and worrying figures. Our percentages of affected children are higher than those described in the United Kingdom¹ and in other studies^{10,11}, possibly due to the methodology used. Firstly, our cohort had 18% of hospitalized patients who suffered a more severe acute infection with more prolonged symptoms. Secondly, we evaluated a significant number of not clearly organic symptoms, such as anxiety, sadness, apathy that are as important as the physical symptoms and may be very disabling for children's lives. Surprisingly, when compared with a control group of children treated during the same period for problems other than COVID-19, a similar percentage of prolonged symptoms was observed, which were fundamentally imprecise symptoms, such as anxiety, insomnia, tachycardia, or dizziness. which may be related to the situation experienced and confinement and not to the SARS-CoV-2 infection. We could say that Long-COVID is characterized by appearing mainly in children over 5 years of age and is especially associated with symptoms such as loss of appetite, asthenia and myalgia, in a similar way to that described in adults.

As other authors have already shown, most children make a full recovery, with symptoms lasting between one and two weeks¹. In our series, most symptoms also have a median duration of 3 - 5 days, with asthenia, anosmia/ageusia, and palpitations lasting about two weeks.

Among our patients, persistent COVID was significantly associated with older age, need for hospitalization and for PICU admission, suggesting that severity may be an important risk factor. It is also worth noting that the existence of a family member affected by Long-COVID was associated with an increased risk of up to 2.8 times in children, suggesting that genetic factors could play a significant role, without being able to rule out that a difficult social situation could be a risk factor. Comorbidities were not a risk factor of persistent symptoms.

Most of long-lasting symptoms as anosmia, ageusia, concentration problems, apathy and anxiety were only assessable in older children, which may be a bias when considering age > 5 years as a risk factor for Long-COVID. In fact, some of these symptoms cannot be attributed with certainty to the SARS-CoV-2 infection and could be partly related to the family situation, the lock-down, lack of social relationships, fear of the situation, etc. This seems the most feasible

theory given that in the control group of children treated for other reasons, these symptoms are equally frequent. It is also striking that parents and children attributed some new symptoms to SARS-CoV-2 infection, that were not frequently associated with COVID-19, such as hair loss, memory loss, constipation or skin lesions, and these symptoms were often very long lasting (median of almost one year). Although it is difficult to be sure that these symptoms are truly caused by the infection, many features of this virus are not still well understood and causality cannot be ruled out.

Some of our strengths are also our limitations; the higher percentage of hospitalized children will undoubtedly determine the duration of the symptoms, including those derived from mental status. We excluded children with asymptomatic SARS-CoV-2 infection, so that we do not know whether symptoms may develop after an initial asymptomatic infection. On the other hand, the control group is one of our strengths, and it can help to characterize the symptoms of Long-COVID in children. The possible symptoms of Long-COVID in children under the age of 5 are difficult to assess. This is a retrospective work and prospective approaches could provide better information.

In conclusion, our study shows that children also suffer prolonged symptoms after COVID-19 infection, directly related to SARS-CoV-2 infection or not, which significantly affect their lives and require specific attention. In our series, Long-COVID is characterized by affecting children over 5 years of age, with asthenia, loss of appetite and myalgia as distinctive symptoms. Therefore, there is a clear need for further research on Long COVID in children.

Figure 1: Prevalence and duration of symptoms in old (> 5 years) and young children.

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Figures

Figure 1

Prevalence and duration of symptoms in old (> 5 years) and young children.