Impact on the nervous system of long COVID-19 infection in children

Impacto en el sistema nervioso de la infección COVID-19 larga en niños

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Abstract

Background The coronavirus disease 2019 (COVID-19) pandemic has had a profound global impact, raising concerns about its long-term effects, particularly neurological complications. While studies have highlighted such complications in adults, there is a paucity of research focusing on children.

Objective To examine the medium- to long-term neurological and cognitive symptoms in 18 year old children and below with positive versus negative COVID-19 antigens and to identify the probable risk factors to promote specific health actions.

Methods An observational study was carried out to determine neurological symptoms in the medium and long terms after COVID 19. A random sample of 124 children, both symptomatic or asymptomatic, tested positive or negative for COVID-19 through swab tests.

Results Neurological symptoms were assessed between 6 to 12 months and 2 years after the infection. Acute symptoms, including headache, anosmia, ageusia, and myalgia, were observed in more than 20% of the children, but they generally resolved within 6 to 12 months. Persistent functional difficulties, such as in studying, paying attention, and socializing, were reported in 3% of the cases. Behavioral symptoms at baseline were noted in 7.8% of children, but they were remitted in most cases, except for those with prior involvement.

Conclusion These findings underscore the need for continued monitoring of children following COVID-19 infection and the importance of tailored health interventions.

Keywords
- Coronavirus
- Infections
- Cognition
- Post-Acute COVID-19 Syndrome
- Child

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Resumen

Antecedentes La pandemia por enfermedad por coronavirus 2019 (*coronavirus disease 2019*, COVID-19, en inglés) ha tenido un profundo impacto global y ha generado preocupación sobre sus efectos a largo plazo, especialmente sobre las complicaciones neurológicas. Si bien los estudios han destacado tales complicaciones en adultos, hay escasez de investigaciones centradas en niños.

Objetivo Examinar los síntomas neurológicos y cognitivos a mediano y largo plazo en niños de 18 años o menos, con antígenos positivos *versus* negativos para COVID-19, e identificar los posibles factores de riesgo para promover acciones de salud específicas.

Métodos Se llevó a cabo un estudio observacional para determinar los síntomas neurológicos en el medio y largo plazo tras COVID-19. Una muestra aleatoria de 124 niños se diagnosticó por tests de saliva. Los tests para COVID-19 podían ser negativos o positivos, en niños sintomáticos o asintomáticos.

Resultados Los síntomas neurológicos se evaluaron entre 6 y 12 meses y 2 años posinfección. Se observaron síntomas agudos como cefalea, anosmia, ageusia y mialgias en más del 20% de los niños, que generalmente se resolvieron en un plazo de 6 a 12 meses. En el 3% de los casos, se informaron dificultades funcionales persistentes, como para estudiar, prestar atención y socializar. Los síntomas conductuales se produjeron en el 7.8% en el momento inicial, pero remitieron en la mayoría de los casos, excepto en aquellos con afectación previa.

Conclusión Estos hallazgos enfatizan la necesidad del monitoreo continuo de niños tras la infección por COVID-19 y la importancia de intervenciones de salud personalizadas.

Palabras clave

- Coronavirus
- Infecciones
- Cognición
- Síndrome de COVID-19 Pós-Aguda
- Niño

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has emerged as one of the most significant public health challenges in recent history, impacting populations worldwide with varying degrees of severity. Public health has faced two key problems generated by this infection during the pandemic: on the one hand, the severity of the respiratory syndrome, which required intensive care and led to an increase in morbidity and mortality; on the other hand, the contagiousness of the condition led to a rapid increase in the number of cases, and saturated the availability of the health system.[1]

This situation produced an impact on health caused by the virus itself, but also on the delay in the treatment of acute diseases due to system saturation (referred to as the second wave of impact). Additionally, there was a third effect motivated by the decompensation of chronic pathologies that did not received the necessary control, and a fourth wave resulting from psychiatric disorders caused by the catastrophic experience and the emotional impact of certain measures, such as quarantine in the long term.

Alongside the respiratory symptoms associated with COVID-19, there has been increasing recognition of its neurological manifestations, particularly in adults. Previous outbreaks of related coronaviruses, such as the outbreaks of severe acute respiratory syndrome (SARS) in China and Middle East respiratory syndrome (MERS) in Saudi Arabia, have demonstrated the potential for neurological complications, highlighting the need for vigilance in monitoring such outcomes.[2] The first reports on COVID-19 showed acute neuropathies, encephalitis, strokes, and cognitive impairment as long-term neurological complications in adults.[3]

Despite this exhaustive theoretical scenario, the virus is considered an acute monophasic entity. While the acute phase of COVID-19 has been extensively studied, less attention has been given to its long-term effects, especially in children. The existing literature has primarily focused on the immediate health impacts and management strategies during the pandemic. However, understanding the medium- to long-term neurological and cognitive sequelae in children is essential for comprehensive healthcare planning and intervention strategies.

Objectives

The primary objective of the present study was to investigate the medium- to long-term neurological and cognitive symptoms in 18 year old children and below following COVID-19 infection compared with negative controls, to promote specific health actions.

We specifically aimed to examine the prevalence and nature of post-COVID-19 clinical features between 6 to 12 months and 2 years after the infection in children, comparing those with positive versus negative antigens. Additionally, we aimed to describe functional impairment, persistence of cognitive signs and behavioral symptoms and comparing the positive and negative cases to develop targeted health interventions.

METHODS

We designed a retrospective descriptive observational study to determine neurological and mental symptoms during the COVID-19 pandemic. A randomized sample of 124 children and adolescents under 18 years of age was selected (age range: 2.7–16.0 years) and tested for COVID-19 in Buenos Aires, Argentina, from September 2020 to October 2021, regardless of whether they were negative or positive, symptomatic or asymptomatic.

In total, 92 families were contacted between 6 and 12 months after the test, and telephone interviews were conducted with the mothers. Neurological symptoms were collected at the onset or during the acute episode. Functional symptoms were validated through the World Health Organization (WHO) Disability Assessment Scales[4] (WHODAS) 6 to 12 months after testing. The medical records of all patients were reviewed after 2 years, with 54 out of 92 with appointments for school or health check-up with their mothers as outpatient clinic. Patient data were anonymized and archived in a centralized database.

Inclusion criteria

- Individuals under 18 years of age with a diagnosis of COVID-19 through molecular biology techniques based on the detection of the viral genome, as stated in a survey answered by their parents.
- Provision of informed consent to participate in the study in accordance with the follow-up protocol of the School Health Program of the Argentinian Ministry of Health between 6 to 12 months after the infection.

Exclusion criteria

- Failure to provide consent for the study procedures.
- Patients not residing in the Autonomous City of Buenos Aires (Ciudad Autónoma de Buenos Aires, CABA, in Spanish).

Cases with persistent symptoms would undergo a neurological and/or neuropsychological assessment protocol. Data were processed with Python software (Python Software Foundation, Wilmington, DE, United States), version 3.8, and the study was approved by the Ethics and Research Committee of Hospitals in the city of Buenos Aires.

RESULTS

Of the total number of patients, 81 children (65%) tested positive for COVID-19. There were no significant differences in age or gender between the positive and negative cases (►**Table 1**). Regarding the socioeconomic level, according to the sociodemographic questionnaire applied through the Graffar Method,[5] 56% corresponded to low and indigent strata, and the rest, to high, medium-high, and medium-low strata.

Neurological symptoms

The most typical acute neurological symptoms, such as headache, anosmia, ageusia, and myalgia, were present in more than 20% of the children (►**Table 2**).

Immediately after COVID-19 infection, the level of functional disability according to the WHODAS[4] showed persistent difficulties in studying, paying attention, social skills, and meeting friends in 3 children out of 92 positive cases, between 6 to 12 months. There were no significant differences between the outpatients and those required hospitalization (►**Table 3**).

Persistence of neurological or behavioral symptoms was reported by 22 (24%) patients between 6 and 12 months after the infection: 16 cases of neurological symptoms, 3 of behavioral symptoms, and 3 of both. Only 2 cases presented persisting symptoms after 2 years. No patient was referred due to new manifestations after 12 months. A comparison of the neurological symptoms of the patients in the acute stage and after the infection is presented in ►**Table 4**.

Cognitive and behavioral symptoms

Behavioral symptoms, such as fatigue, anxiety, or sadness, appeared during the acute episode and persisted in 8 patients, and only remained in 2 cases: these were problems meeting with friends or subjective impairment in learning between 6 and 12 months after the infection (►**Table 4**). One boy under psychiatric treatment before the pandemic received a diagnosis of borderline personality disorder at the last check-up 2 years later. One baby presented delay in language acquisition, which persisted at the last check-up. There was one case of a patient with learning problems who required support.

Table 1 Sociodemographic characteristics of the study population

Characteristics		Total	Positive COVID: outpatients	Positive COVID: hospitalized patients	Negative COVID	*p*-value[a]
N (%)		124 (100%)	81 (65%)	11 (9%)	32 (26%)	–
Age in years (range)		10 (2.7–16.0)	10 (7.6–14.5)	10 (2.7–16.0)	9 (5.2–12.1)	0.4
Self-perceived gender: n (%)	Female	59 (48%)	39 (48%)	7 (64%)	13 (41%)	0.4
	Male	65 (52%)	42 (52%)	4 (36%)	19 (59%)	
Male/female ratio		1.1/1	1.1/1	1.1/1	1.1/1	0.4

Abbreviation: COVID, coronavirus disease.
Note: [a]Kruskal-Wallis rank-sum test; Pearson Chi-squared test; Fisher exact test.

Table 2 Neurological symptoms in patients positive for coronavirus disease 2019

Symptoms	Total (N = 97): n (%)	Outpatients (n = 81): n (%)	Hospitalized patients (n = 11): n (%)	*p*-value[a]
Headache	24 (26%)	19 (23%)	5 (45%)	0.15
Anosmia	20 (22%)	16 (20%)	4 (36%)	0.2
Ageusia	12 (13%)	9 (11%)	3 (27%)	0.2
Myalgias	7 (7.6%)	7 (8.6%)	0 (0%)	0.6
Dizziness	2 (2.2%)	1 (1.2%)	1 (9.1%)	0.2
Paresthesias	2 (2.2%)	1 (1.2%)	1 (9.1%)	0.2
Hypoesthesia	0 (0%)	0 (0%)	0 (0%)	–
Dysautonomia	2 (2.2%)	1 (1.2%)	1 (9.1%)	0.2
Language	2 (2.2%)	1 (1.2%)	1 (9.1%)	0.2
Drowsiness	2 (2.2%)	2 (2.5%)	0 (0%)	> 0.9
Insomnia	3 (3.3%)	3 (3.7%)	0 (0%)	> 0.9
Asymptomatic	0 (0%)	0 (0%)	0 (0%)	–

Note: [a]Fisher exact test; Wilcoxon rank-sum test.

Table 3 Results according to the World Health Organization Disability Assessment Scale (WHODAS)

Domains	Total (N = 124): n (%)	Positive COVID (outpatients: n = 81): n (%)	Positive COVID (hospitalized patients: n = 11): n (%)	Negative COVID (n = 32): n (%)	*p*-value[a]
Ambulation: no change	105 (98%)	74 (97.4%)	11 (100%)	20 (100%)	> 0.9
Ambulation: worsened and gradually improved	2 (1.9%)	2 (2.6%)	0 (0%)	0 (0%)	
Learning new tasks: no change	105 (99%)	74 (99%)	11 (100%)	20 (100%)	> 0.9
Learning new tasks: worsened and did not improve	1 (0.9%)	1 (1.3%)	0 (0%)	0 (0%)	
Social gatherings: no change	104 (98%)	74 (99%)	10 (91%)	20 (100%)	0.2
Social gatherings: worsened and gradually improved	1 (0.9%)	1 (1.3%)	0 (0%)	0 (0%)	
Social gatherings: worsened and did not improve	1 (0.9%)	0 (0%)	1 (9.1%)	0 (0%)	
Attention: no change	105 (99%)	74 (99%)	11 (100%)	20 (100%)	> 0.9
Attention: worsened and did not improve	1 (0.9%)	1 (1.3%)	0 (0%)	0 (0%)	
Ambulation for 1 km: no change	103 (98%)	72 (97%)	11 (100%)	20 (100%)	> 0.9
Ambulation for 1 km: worsened and gradually improved	2 (1.9%)	2 (2.7%)	0 (0%)	0 (0%)	
Bathing: no change	105 (100%)	75 (100%)	10 (100%)	20 (100%)	
Getting dressed: no change	105 (100%)	75 (100%)	10 (100%)	20 (100%)	
Meeting new people: no change	104 (96%)	74 (96%)	10 (91%)	20 (100%)	0.5
Meeting new people: worsened and gradually improved	2 (1.9%)	2 (2.6%)	0 (0%)	0 (0%)	
Meeting new people: worsened and did not improve	2 (1.9%)	1 (1.3%)	1 (9.1%)	0 (0%)	
Meeting friends: no change	105 (98%)	75 (97%)	10 (100%)	20 (100%)	> 0.9
Meeting friends: worsened and did not improve	2 (1.9%)	2 (2.6%)	0 (0%)	0 (0%)	
Day-to-day schoolwork: no change	105 (99%)	74 (99%)	11 (100%)	20 (100%)	> 0.9
Day-to-day schoolwork: worsened and did not improve	1 (0.9%)	1 (1.3%)	0 (0%)	0 (0%)	
Total of "worsened and did not improve" answers	8				

Abbreviation: COVID, coronavirus disease.
Note: [a]Fisher exact test, hospitalized patients versus outpatients.

Table 4 Comparison between acute and long coronavirus disease 2019 (COVID-19)

COVID positivity and symptoms		Total: N (%)	6-12 months after COVID: n (%)	2 years: n (%)
COVID positive		92 (100%)	92 (100%)	83 (100%)
Anosmia		20 (22%)	2 (1.6%)	0
Myalgias		7 (7.6%)	3 (2.4%)	0
Ageusia		12 (13%)	0	0
Headache		24 (26%)	7 (5.6%)	0
Dizziness		2 (2.2%)	2 (1.6%)	0
Paresthesias		2 (2.2%)	6 (4.8%)	0
Hypoesthsias		0 (0%)	0	0
Disautonomy		2 (2.2%)	0	0
Drowsiness		2 (2.2%)	1 (0.8%)	0
Insomnia		3 (3.3%)	2 (1.6%)	0
Dysphagia		0	2 (1.6%)	0
Language		1 (1,1%)	1	1
Tinnitus		0	1 (0.8%)	0
Visual complaints		2 (2.2%)	1 (0.8%)	0
Behavioral	Meeting new people	2 (1.9%)	1 (0.8%)	1 (0.8%)
	Meeting friends	2 (1.9%)	0	0
	Day-to-day schoolwork	1 (0.9%)	0	0
	Overall behavior	1 (0.9%)	1 (0.8%)	0
	Fatigue	3 (2.4%)	3 (2.4%)	0
	Anxiety	3 (2.4%)	3 (2.4%)	0
	Sadness	1 (0.8%)	1 (0.8%)	0
	Anhedonia	1 (0.8%)	1 (0.8%)	0
	Learning disorders	1 (0.9%)	1(0.8%)	1(0.8%)
	Language	0	1 (0.8%)	1(0.8%)
	Social skills: personality	1 (0.9%)	1 (0.8%)	1(0.8%)
	Physical tiredness	2 (1.6%)	2 (1.6%)	0

DISCUSSION

The findings of the present study contribute to our understanding of the medium- to long-term neurological and cognitive symptoms in children following COVID-19 infection. While acute symptoms were common, they tended to resolve within the first year after the infection, with few cases of persistent functional difficulties or behavioral symptoms.

Neurological manifestations both at the onset or during the COVID-19 infection have been associated with a more severe disease, as demonstrated by a longer hospital stay, and higher in-hospital death rate or sequelae at discharge.[6]

A study reported[7] that postacute COVID-19 syndrome (PACS) was frequent, occurring in more than 30% of adults 3 months after the infection; the psychiatric exacerbated later, between 3 and 6 months after the infection. A revision from Japan showed that in one multicentric research conducted in the United Kingdom half of the patients (48.8%) did not feel fully recovered from COVID-19 1 year after the infection; at 14 to 15 months from COVID-19 onset, there was improvement in olfactory and taste disorders, but no change in central dysfunction, brain fog, numbness, dizziness, or headache.[8]

There are few reports after 12 months of follow-up in children, like the present study. One multicentric study[9] showed 21% of neurological syndromes in children; another study[10] reported symptoms such as headache, anosmia, dysgeusia, myalgia and muscle weakness. There is limited data on populations in conditions of socioeconomic adversity. The present study provides information on a population of children, and medium and low economic levels prevailed in the sample.

Cognitive symptoms such as difficulty in concentration, brain fog, and confusion persisted after 2 weeks of discharge according to one study.[10] In the sample of the present study, according to the level of functional disability on the WHO-DAS, only 3% had persistent difficulties between 6 to 12 months after the infection.

The main subjective problems involved paying attention and meeting friends. The hypothesis that long COVID might in part correspond to a functional disorder remains as a confounder in mild cases, which did not require hospitalization.[11]

There were no significant differences between the outpatients and the subjects who required hospitalization. We did not find other studies that assessed functional disability during this period.

Regarding cognition, the question about neurological dysfunction in the long term was also addressed in a few reports. A study[12] involving a neuropsychological assessment of 25 children who had had COVID-19 showed that they had evolved with impairment in attention, memory and visuomotor skills, although the differences were not significant. In the sample of the present study, only 1 patient aged 2 years presented a language delay that persisted at the last check-up 24 months later.

In the follow-up of children whose mothers tested positive for COVID during pregnancy, development scales showed a tendency towards worse motor and personal social skills compared to controls in the short term.[13]

One study[14] reported that behavioral symptoms included sleep problems and anxiety in more than 20% of adults, as well as depression and increased risk of suicide, which persisted within the first month of discharge. One review[15] described the persistence of fatigue, memory, and attention problems in adults one year after the infection; however, we did not find any reports concerning children. Our group observed less persistence of symptoms compared to reports from children and adolescents[15], where neurological signs were noted in 13% of cases, alongside psychiatric symptoms. We found a rate of 3% of behavioral problems, such as difficulty in meeting with people or friends, or difficulties studying. There was only one patient with severe symptoms who was under psychiatric treatment before the pandemics and was later diagnosed with borderline personality disorder at the last check-up, after 2 years of the infection. Only in two patients' fatigue and anxiety persisted 2 years later. These symptoms have been associated with the significant changes in the habits of adolescents during the pandemic, such as the development of sedentary lifestyles, lack of social contact, and poor diet.[16] One year after the pandemic, one of our patients, a teenager was referred for loss of appetite. She had no history of dysgeusia or anosmia during the infection, as suggested by studies about anorexia, which is sometimes associated to taste issues.[17]

The risk factors for the persistence of behavioral problems were considered more in females, those with multisystemic disease, aged 14 years,[18] with a body mass index of 30 kg/m^2 or greater (odds ratio [OR]: 0.50), and those requiring mechanical ventilation (OR: 0.42).[8] Requirement of intensive care unit is negative not only for COVID-19 patients but also for those with other respiratory diseases.[19] In the sample of the present study, there was no difference between patients who were hospitalized and those who were not. Since the sample was the present study was randomly selected based on laboratory screening for antigens, we consider that it contains a lower level of bias.

The results of the present study are in line with those of the existing literature on neurological manifestations in children, but we emphasize the need for continued monitoring and targeted interventions, particularly in cases with prior involvement or persistent symptoms.

In conclusion, the current study highlights the prevalence and nature of medium- to long-term neurological and cognitive symptoms in children following COVID-19 infection. Acute neurological symptoms were found in more than 20% of the children, most often headache, anosmia, ageusia, and myalgia. While most acute symptoms resolved within the first year after the infection, a small subset of children experienced persistent functional difficulties and behavioral symptoms.

Behavioral symptoms at baseline occurred in 7.8% of the sample and persisted in 3%, except in patients with prior involvement. Difficulties were occasionally persistent at a functional level: learning, paying attention and socializing. No significant differences were observed between the outpatients and the subjects who required hospitalization. These findings underscore the importance of ongoing monitoring and tailored health interventions to support the well-being of children affected by COVID-19.

Authors' Contributions

NG: investigation, project administration, supervision, validation, writing – original draft, and writing – review & editing; AT: conceptualization, data curation, and methodology; IC: formal analysis, methodology, resources, and software; AC, BR, JMF, SV, ML, IW: investigation; and RA: conceptualization, data curation, investigation, methodology, supervision, and validation.

Conflict of Interest

The authors have no conflict of interest to declare.

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