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Review Article

Neurological manifestations of COVID-19 in the pediatric population - a literature review and development of clinical cases for didactic purposes

Manifestações neurológicas da COVID-19 na população pediátrica - revisão de literatura e desenvolvimento de casos clínicos com finalidades didáticas

Eduarda Padilha[1], Adriano Yacubian Fernandes[2]

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ABSTRACT: The COVID-19 is an acute respiratory syndrome with different reported non-respiratory symptoms, neurological manifestations included. The nervous system impairment during the infection occurs in adults and children, yet the pediatric population has particularities in the clinical course of the disease. We discuss the neurological manifestations of COVID-19 in children, developing cases to be applied in disciplines within a "problem-based" learning methodology. The proceedings of the research were developed with undergraduate medicine students in mind: a literature review on the topic was performed; then observed by the selection of 16 articles reviewed, summarized and discussed. This paper discusses proceedings, challenges and outcomes, of each stage of the research's agenda. In the literature review, we found many neurological manifestations in the pediatric population. Other aspects relevant to the topic were also found, such as: association of comorbidities, alterations in complementary exams, prognoses and pathophysiological hypotheses. Based on the findings, we created three clinical cases for application in undergraduate studies. We concluded that the topic has great clinical and learning importance, yet more research is needed on the subject.

Keywords: Neurologic manifestations; COVID-19; Adolescent; Child; Infant; Problem-based learning; Education, medical

RESUMO: O COVID-19 é uma síndrome respiratória aguda com diferentes sintomas não respiratórios relatados, incluindo manifestações neurológicas. O comprometimento do sistema nervoso durante a infecção ocorre em adultos e crianças, porém a população pediátrica apresenta particularidades no curso clínico da doença. Discutimos as manifestações neurológicas da COVID-19 em crianças, desenvolvendo casos para serem aplicados em disciplinas dentro da metodologia baseada em problemas. A pesquisa foi desenvolvida tendo em vista os graduandos em medicina: foi realizada uma revisão da literatura sobre o tema; em seguida, observado pela seleção de 16 artigos revisados, resumidos e discutidos. Este artigo discute os procedimentos, desafios e resultados de cada etapa da agenda de pesquisa. Na revisão da literatura encontramos diferentes manifestações neurológicas na população pediátrica. Outros aspectos relevantes ao tema também foram encontrados, como: associação de comorbidades, alterações em exames complementares, prognósticos e hipóteses fisiopatológicas. Com base nos achados, criamos três casos clínicos para aplicação na graduação. Concluímos que o tema tem grande importância clínica e de aprendizado, mas ainda são necessárias mais pesquisas sobre o assunto.

Palavras-chave: Manifestações neurológicas; COVID-19; Adolescente; Criança; Lactente; Aprendizagem baseada em problemas; Educação médica.

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1. Universidade de São Paulo. https://orcid.org/0000-0002-3183-4601. E-mail: eduarda.padilha@usp.br;
2. Universidade de São Paulo e Universidade Estadual Paulista Júlio de Mesquita Filho. https://orcid.org/0000-0002-2915-1852. E-mail: yacubian@usp.br
Correspondence: Alameda Dr. Octávio Pinheiro Brisolla, Quadra 9 - Jardim Brasil, Bauru - SP

INTRODUCTION

The COVID-19 pandemic is one of the major public health issues that humanity has faced over these last decades. Until now, over 500 million cases have been reported, and over 6 million deaths have been accounted[1]. The coronavirus 2019 disease (COVID-19) is an infectious disease characterized by fever, cough, dyspnea, chills, persistent tremor, muscle pain, headache, and sore throat, and caused by the SARS-CoV-2 virus. Although this pathogenic agent is defined primarily as respiratory, over these years of the pandemic, we observed the involvement of other systems with their respectively clinical manifestations. Among them, the impairment of the nervous system (central and peripheral) has shown to be a relevant clinical phenomenon and wide studied by the literature. Over 80% of hospitalized patients with COVID-19 presented some neurological sign or symptom at some point in the clinical evolution[2]. Some of the most common neurological manifestations reported were: anosmia/ageusia, myalgia, headache, encephalopathy and dizziness[2].

The impairment of the nervous system was described in different ages, including in the pediatric population, which is known to present a particular clinical course of the disease. Compared to adults, children and adolescents have less severity and develop the form mild or asymptomatic – although they can transmit the disease. About 2% of the children with COVID-19 are hospitalized and less than 1% die[3]. However, even with the less severity of the cases, it was reported different neurological manifestations in this population. In 9 international case series, it was found a frequency of 150 in 4190 patients[4].

This data supports that neurological manifestations of COVID-19 are an important aspect of the disease, in adults and children. Therefore, this topic must be discussed by the undergraduate, once the pandemic continues and the physiopathologic aspects help in the understanding of infections and their development.

So, this work has the object of studying the neurological manifestations of COVID-19 in the pediatric population, understanding the relevance of the topic and its importance to medical undergraduates.

OBJECTIVES

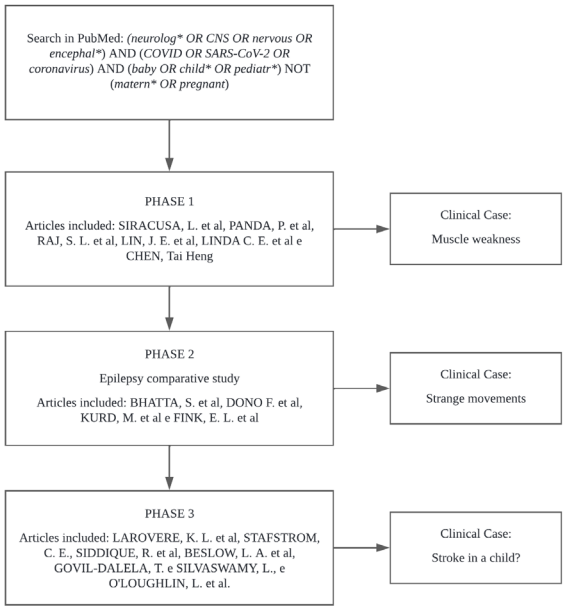
The general objective of this work is the production of clinical cases on the neurological manifestations of COVID-19 in the pediatric population for didactic application in the medical course. The specific objectives are: (1) to perform a systematic literature review on the neurological manifestations of COVID-19 in the pediatric population and (2) to create clinical cases on the same theme for application in tutoring teaching environments, and skills labs.

METHODS

The first step of the work was the definition of its PCC (population, concept and context) as pediatric population (population) - individuals from 0 to 21 years of age -, clinical manifestations (concept) - clinical signs and symptoms caused by injury or nervous system dysfunction –, and COVID-19 (context) – infectious pathology caused by the SARS-CoV-2 virus.

We performed this work in three phases with a different focus of study. The first phase aimed to study the general neurological manifestations of COVID-19 in the pediatric population; the second, the specific neurological manifestation of epilepsy in the same population and context, and, finally, the last phase also focused on general manifestations but based on more recent review texts on the subject. Thus, in each phase a brief literature review was carried out and, at the end of it, a clinical case on the topic was produced (Table 1).

Table 1 - Methodology Flowchart



For the literature review, a search was performed in the PubMed database with the following terms: "(neurolog* OR CNS OR nervous OR encephal*) AND (COVID OR SARS-CoV-2 OR coronavirus) AND (baby OR child* OR pediatric*) NOT (matern* OR pregnant)". The choice of articles for inclusion had as an inclusion criterion the relevance of the article for this work according to the proposed objectives. The selected studies were read in full, summarized and presented at weekly team meetings. It is worth mentioning that, in the second phase, a brief comparative study was carried out on the topic of epilepsy,

based on the articles analyzed in the previous phase.

In each of the phases, after the literature review, clinical cases were produced on the topic with the purpose of application in undergraduate. For the construction of the cases, the learning objectives were initially established with the most prevalent issues on the neurological manifestations of COVID-19 in the pediatric population in mind, found in the literature review, and taking into account their relevance in the context of undergraduate medicine. Then, the clinical case was created with credible data, addressing the previously defined objectives. To this end, additional materials from the medical literature were used and referenced at the end of each case. Finally, a title that summarizes it was given to the case and, at the same time, instigates curiosity about the topic. Thus, every case was created with the following components: title, clinical case, learning objectives and references.

RESULTS

Literature review

Neurological manifestations are an important aspect of the development of COVID-19 in the pediatric population. An article points to a 34% incidence of neurological involvement in children affected by the disease[5]. Thus, it is justified the importance of the study on the subject, objective of this work, which from the analysis of 16 articles proposes to carry out a brief review of the literature. The main aspects of each of the articles read are summarized in Table 2.

Table 2 - Literature review findings

Reference	Neurological manifestations described	Discussion
Siracusa et al.[6]	**Neurological symptoms:** headache, altered mental status, seizure, muscle weakness, and meningismus **Neurological Manifestations**: cerebrovascular accident, reversible splenic injury, GBS, benign intracranial hypertension, meningoencephalitis, autoimmune encephalitis, ADEM, cranial nerve involvement, transverse myelitis, encephalopathy with bilateral thalamic lesion, and fatal brain edema	Minority of cases related to comorbidity. Expressive relationship between the development of neurological manifestations and the course of MIS-C. Division into three scenarios: neurologic involvement during COVID-19, neurologic involvement beginning with recovery from COVID-19, neurologic involvement during MIS-C. The most common radiological alteration was in the splenium of the corpus callosum. Prognoses, in general, favorable.
Panda et al.[7]	Encephalopathy, seizure, meningeal signs, cranial nerve palsy, and vision changes	Most of the neurological manifestations presented were nonspecific. Patients with specific manifestations had more severe symptoms of COVID-19. Patients with MIS-C had a higher prevalence of neurological symptoms.
Raj et al.[8]	Acute febrile encephalopathy with febrile seizure associated with MIS-C and febrile status epilepticus	Important relationship between the development of neurological manifestations and the course of MIS-C.
Lin et al.[9]	Headache, fatigue or malaise, altered mental status, weakness, seizures, sixth cranial nerve palsy, intracranial hypertension, dysgeusia and ageusia, stroke, and encephalopathy	Relationship of the development of neurological manifestations with the course of MIS-C. Radiological changes found in the splenium of the corpus callosum and in the thalamic nucleus. No child had positive viral RNA in cerebrospinal fluid. Hypothesis of a milder course of neurological manifestations in children due to a more attenuated picture of lung disease and lower prevalence of comorbidities. Predominance of the immune-mediated inflammatory response in children compared to adults. Main pathophysiological hypotheses: direct infection of the NS and its vasculature, secondary inflammatory response, indirect effects of cardiovascular complications and hypoxia due to respiratory failure.
Lindan et al.[10]	Myelitis, neuritis, anosmia, labyrinthitis, cauda equina enlargement, Guillain-Barré syndrome, thromboembolic and vascular findings, seizure, myositis	The most common neuroimaging manifestation was of an immune-mediated pattern. Patients with COVID-19 and co-infections were the most severe patients followed by death in its entirety. The most common change in children with MIS-C was in the splenium of the corpus callosum. Overall favorable prognosis, with the majority with full recovery or minimal neurological sequelae.
Chen[5]	Headache, meningism, and altered mental status	Relationship of the development of neurological manifestations with the course of MIS-C. Possible impairment after the active phase of the disease. No viral findings in cerebrospinal fluid. Radiological findings of cerebral edema.

continue

Table 2 - Literature review findings *continuation*

Reference	Neurological manifestations described	Discussion
Bhatta et al.[11]	Afebrile isolated seizure	Single clinical presentation of COVID-19.
Dono et al.[12]	Acute symptomatic epileptic seizures and status epilepticus	Most common associated symptoms were respiratory and gastrointestinal symptoms. Better prognosis and survival of younger patients.
Kurd et al.[13]	Seizures and status epilepticus	Seizures may be the initial and primary manifestation of COVID-19, especially in those with a history of neurological disorders. Possible relationship between older ages and seizures.
Fink et al.[14]	Headache, acute encephalopathy, seizure/status epilepticus, weakness, dizziness, anosmia, ageusia, delirium, visual disturbance, ataxia, numbness, syncope, coma, paresthesia, meningitis/encephalitis, sympathetic storm/dysautonomia, cardiac arrest, stroke, neuropathy, myelopathy and others (coacute neurological condition, acute psychosis, photophobia/phonophobia, cranial nerve abnormality, hypotonia, papilledema, dysarthria, meningismus, arthralgia, dysphagia, Moyamoya disease, and unspecific)	Advanced age, MIS-C, pre-existing neurological and metabolic condition, and non-neurological symptoms associated with increased risk for neurological manifestation.
Larovere et al.[4]	Acute CNS infection, central demyelination disorder, ischemic or hemorrhagic stroke, Guillain-Barré syndrome, and severe encephalopathy	Common neurological involvement in children with COVID-19. Most previously healthy patients, but those with neurological impairment had more preexisting conditions. Mortality of approximately 3.8%, with 78.6% related to neurological involvement.
Stafstrom[3]	Anosmia/ageusia, demyelinating disease, cerebrovascular disease, encephalitis, altered mental status, seizure and headache	Study focus on children up to 1 year old. Vertical transmission as an unlikely hypothesis. Manifestations divided into acute, post-acute and long-term. Low mortality in children. Need for studies to actually establish the relationship between neurological manifestations and infection, if it actually exists. Main pathophysiological hypotheses: direct neuroinvasion and hyper-inflammatory response. Impact on child development.
Siddique et al.[15]	Headache, encephalopathy, mental status changes, seizure, coma, demyelinating disorder, dysgeusia or ageusia, aseptic meningitis, stroke, dysphagia, cerebellar ataxia, axial hypotonia, vertigo, and peripheral neuropathy	Main pathophysiological hypotheses: axonal transport, via leukocytes and via endothelium. Lesser impact on the pediatric population would be due to: differential expression of ACE2, fewer comorbidities and predisposition to an inflammatory state – tendency to decline in the innate immune system with age. Possible impact of mental status of pregnant women with COVID-19 on child development. Increased risk of stroke, PNS disorders, delirium, encephalopathy and headache. No findings in cerebrospinal fluid.
Beslow et al.[16]	Ischemic and hemorrhagic stroke	Questioning the real relationship between the infection and the clinical picture.
Govil-Dalela, Sivaswamy[17]	Meningitis, encephalitis, encephalopathy, seizure, stroke, possible developmental delay, anosmia/ageusia, Guillain-Barré syndrome, muscle damage, and rhabdomyolysis	Main pathophysiological hypotheses: direct invasion via ACE-2 to neurons and endothelial cells; retrograde transmission via the olfactory bulb and cranial nerves; systemic viremia with breakdown of the blood-brain barrier and neuroinflammation; and endotheliopathies by direct invasion or immune-mediated cascade. Main radiological findings: acute lesions in the splenium of the corpus callosum and intramyelinic edema. Most CSF negative analysis for SARS-CoV-2. Findings of axonal lesions, perivascular lymphocytic infiltration, neuronal loss and inflammatory interstitial changes. Treatment according to the manifestation.
O'loughlin et al.[18]	Cerebrovascular disease, encephalitis, encephalopathy, Guillain-Barré syndrome and severe neurological manifestations associated with MIS-C.	Main pathophysiological hypotheses: direct neuroinvasion or activation of the immune system. Stroke and encephalopathy as predominant syndromes. Important relationship with MIS-C.

[a] The article defines an age group, however, it was included in this work due to the overview of status epilepticus in the context of COVID-19 and because it highlights the important relationship between lower age groups and better prognoses.

Clinical cases

From the literature review described above and the study of the medical literature on the subject, three clinical cases were created with different main subjects, yet, having the neurological manifestations of COVID-19 in the pediatric population as a common theme.

In the first phase of the project, the case "Muscular Weakness" was created (Table 3), which focuses on the neurological manifestations that lead to the loss of limb strength, reported in some children with COVID-19[6,9,10,14,15].

In the second phase, which had epilepsy as its subject, the case "Strange Movements" was produced (Table 4). Seizures were common findings among pediatric patients infected with SARS-CoV-2[3,6-17] and therefore its relevance in being approached in a teaching context.

The last case, "stroke in a child?" (Table 5), created in the last phase of the project, has stroke as its central discussion, described as an important neurological manifestation of COVID-19 in children[3,4,6,9,10,14,16,17,18]. In addition, the stroke in children study at undergraduation is extremely important to improve the treatment of an emergency, which can be difficult to diagnose given the mimicry of symptoms of other pathologies in this specific population[19].

Table 3 – Clinical Case: muscle weakness

Title	**Muscle weakness**
Clinical Case	Enzo, 10 years old, born and resident in São Paulo, arrived at the Bela Vista Emergency Care Unit, accompanied by his mother, Ana. She reported that the two came to Bauru a few months ago, during the COVID-19 pandemic, to keep her mother company and to have more space, since in São Paulo they lived in a small apartment and now both are in a home office. . However, for the past two days, Enzo has complained of weakness in his lower limbs. Initially she thought it was normal because he now spent the day playing in the street, whereas before he only played video games. However, this situation worsened and evolved with fever and headache, hence her decision to take her child to the UPA. Asked if anyone close to her had COVID-19, Ana replied that she did not know, but that in the last few days she and her mother had a cold. When performing the physical examination in Enzo, you found: RE, oriented, acyanotic, anicteric, hydrated, height = 1.35m, weight = 30kg, febrile (38.4º), HR = 80 bpm, RR = 22 ipm, BP = 109 x 58 mmHg. Normal cardiovascular system and presence of snoring on pulmonary auscultation. In the neurological examination, the patient showed the different reflexes and when performing the muscle strength test you confirmed the weakness of the lower limbs. From these results you ordered a test for SARS-CoV-2 which came back positive. He also requested brain and spinal magnetic resonance imaging, which showed the following results: mass effect in the right frontal lobe on FLAIR imaging in infantile MRI, and mildly expensive cord on the T2-weighted imaging of the spine. Given the hypothesis of long-segment myelitis due to SARS-CoV-2 infection, you started treatment with high-dose steroids and referred the patient for admission. After two weeks, the patient improved and was discharged.
Learning objectives	1. Understand the steps of the neurological physical examination and relate to possible findings. 2. Know how to interpret the patient's imaging tests, being able to identify the anatomical structures present. 3. Understand the mechanisms that cause muscle weakness, especially in the patient's condition. 4. Relate SARS-CoV-2 viral infection to muscle weakness. 5. Understand the therapeutic mechanism of corticosteroids in the.
References	Lindan CE, Mankad K, Ram D, Kociolek LK, Silvera VM, Boddaert N, et al. Neuroimaging manifestations in children with SARS-CoV-2 infection: a multinational, multicentre collaborative study. Lancet Child Adolesc Heal. 2021;5(3):167-77.

Table 4 – Clinical Case: Strange movements

Title	**Strange movements**
Clinical Case	Rafael, 11 years old, born and resident in Bauru, arrived at the Bela Vista Emergency Care Unit, accompanied by his father, after losing consciousness and making "strange movements". Upon admission, Rafael is drowsy and confused. You then talk to the father to glean more details of the story. He reports that he was in the living room watching TV with his wife while his son was doing his homework at the dinner table when he suddenly screamed. When they looked, they saw that Rafael had fallen to the ground, had lost consciousness and was stiff; and soon afterwards he began to contort his extremities. The two were very worried about what they saw, a feeling that was exacerbated since their son was very confused and sleepy after the episode. So he decided to rush his son to the UPA. He reports that his wife wanted to come, however, as she has COVID-19, they thought it was best for her to stay home. When questioning about the duration of the episode, the father said that it lasted around a minute. Considering the hypothesis that the episode was an epileptic seizure and that the patient has epilepsy, you ask the father about other similar episodes. He informs that three years ago the son also had an episode of "strange movements" at school and was taken to the UPA, and the doctors said it had been a seizure. However, as this never happened again, they didn't bother to go back to the doctor or see a specialist. On physical examination, you note: GER, disoriented, acyanotic, anicteric, hydrated, HR = 92 bpm, RR = 15 ipm, BP = 100 x 65 mmHg, Temperature = 37°C. Normal cardiovascular system. In the neurological evaluation, you notice the patient disoriented in space and time, with cognitive difficulties (memory, language, attention and concentration) and drowsiness. In view of the patient's condition, you hospitalize the patient and request a blood count, sodium, potassium and a CT scan of the head. In addition, because the mother has COVID-19, she requests an oropharynx swab for SARS-CoV-2. The blood count is normal, as are the electrolytes (Na - 137 mmol/L and K - 3.5 mmol/L). Cranial CT also shows no changes. The COVID test was positive. You then refer the patient for an EEG and follow-up with a neurologist.
Learning objectives	1. Discuss the patient's syndromic, topographic and etiological diagnoses. 2. Differentiate epileptic seizures and epilepsy. 3. Understanding the pathophysiology of epilepsy. 4. Understand how epilepsy is diagnosed and its classifications. 5. Know the main pharmacological therapies for the treatment of epileptic seizures and epilepsy. 6. Discuss how SARS-CoV-2 infection may be related to the patient's condition.
References	Bhatta S, Sayed A, Ranabhat B, Bhatta RK, Acharya Y. New-Onset Seizure as the Only Presentation in a Child With COVID-19. Cureus. 2020;12(6):10-3. Kurd M, Hashavya S, Benenson S, Gilboa T. Seizures as the main presenting manifestation of acute SARS-CoV-2 infection in children. Seizure. 2021;92:89-93. https://doi.org/10.1016/j.seizure.2021.08.017 Nitrini, R and Bacheschi, LA. A neurologia que todo médico deve saber. 3rd ed. São Paulo: Atheneu; 2003 [20]

Table 5 – Clinical Case: Stroke in a child?

Title	**Stroke in a child**
Clinical Case	Marcela, 5 years old, born and resident in Bauru, arrived at the Central Emergency Room in Bauru after a seizure, accompanied by her mother, Carolina. The mother reported that, about 40 minutes ago, she was playing with her daughter when Marcela lost strength on her right side, dropping a toy she was holding, and then had a seizure that made her fall to the floor. After the episode, Marcela's right side continued to be weak and she began to complain of a headache and was irritable and sleepy. Asked about the duration and other episodes of crisis, Carolina stated that the crisis lasted about 1 minute and was the first time it had occurred. The doctor on duty asked about the patient's personal background and the mother said that Marcela was a healthy child, without any associated illness, but that she had COVID-19. She had been diagnosed by PCR 2 days ago, after a picture of flu-like syndrome. On physical examination: GER, disoriented, acyanotic, anicteric, hydrated, height = 1.10 m, weight = 19 kg, afebrile, HR = 75 bpm, RR = 22 ipm, BP = 105 x 70 mmHg. Normal cardiovascular and pulmonary systems. In the neurological examination, the patient presented: disorientation, irritability, drowsiness, confused speech, right hemiparesis, preserved reflexes and right hemihypoesthesia. The doctor then raised the hypothesis that the patient had suffered from an epileptic seizure with associated Todd's palsy, however, he requested a blood glucose test - to rule out the possibility of a hypoglycemic condition - and an electrolyte test to rule out possible hydroelectrolytic disorders. About 3.5 hours after admission, results came in with a blood glucose of 80 mg/dl and normal electrolytes. Upon returning to re-evaluate the patient, he noticed a worsening of the general condition. Marcela started to present hemiplegia on the right side, including central facial paralysis, with difficulty in verbalization. Characteristic picture of cerebrovascular accident. Immediately, he requested a referral to the Base Hospital, next to the Central Emergency Room and a reference for stroke care in the city, so that a CT scan of the skull could be performed and the Stroke Protocol started. After performing the CT with normal results and discarding the diagnosis of hemorrhagic stroke, the new physician responsible for the case at the Base Hospital, questioned himself about the conduct to be taken, considering that the therapeutic window for performing thrombolysis had already passed. and since early seizures are relative contraindications due to the differential diagnosis of post-seizure paralysis.
Learning objectives	1. Understand the clinical picture of Ischemic Stroke (CVA) and its particularities in the pediatric population. 2. Discuss the main differential diagnoses of stroke, especially in children, and how it is possible to differentiate them during care. 3. Discuss risk factors for childhood stroke and how SARS-CoV-2 infection may be associated with the condition. 4. Understanding the management of patients with ischemic stroke.
Reference	Brickle I. Normal CT brain – 4-year-old. Radiopaedia.org. Available at: https://radiopaedia.org/cases/normal-ct-brain-4-year-old?lang=us[21] Ferriero DM, Fullerton HJ, Bernard TJ, Billinghurst L, Daniels SR, Debaun MR, et al. Management of stroke in neonates and children: a scientific statement from the American Heart Association/American stroke association. Stroke. 2019;50:51-96.

DISCUSSION

Neurological manifestations resulting from COVID-19 can be classified according to their specificity and the time in the course of the disease in which it occurred. Thus, manifestations are divided into nonspecific, such as myalgia, fatigue, headache and weakness, and specific, such as encephalopathy, seizures and stroke. Nonspecific manifestations are more prevalent than specific ones, occurring in 16% of cases as opposed to 1%, respectively[7]. Among the nonspecific symptoms, headache stands out, being the most common involvement, presenting in about 28% of pediatric patients with COVID-19[9]. Another important classification of manifestations is the moment in the development of the disease when the symptoms appeared, which may be in the acute phase of the disease,

in the subacute phase, or after the clinical manifestation (prolonged-COVID). This last phase shows a growing concern due to the persistence of the pandemic[3].

Another fundamental aspect in the understanding of neurological involvement is the Multisystem Inflammatory Syndrome Children (MIS-C), characterized by its clinical picture similar to toxic shock syndrome or Kawasaki disease and defined by children and adolescents (up to 19 years) with fever for 3 days or more, with at least two of the following findings: (1) bilateral non-purulent rash or conjunctivitis or mucocutaneous inflammatory signs, (2) hypotension or shock, (3) myocardial dysfunction or pericarditis, or valvulitis or coronary abnormality, (4) evidence of coagulopathy, (5) gastrointestinal problems; and elevated inflammatory markers, with no symptoms of another obvious inflammatory cause and evidence of COVID-19 (WHO). This syndrome is closely related to SARS-CoV-2 infection in children and possible neurological complications. Children with COVID-19-associated MIS-C are not only at greater risk of developing manifestations, but are more often admitted to the ICU and for longer[14].

The neurological manifestations described in the analyzed articles were: headache, altered mental status, ageusia/anosmia, seizures, muscle weakness, meningismus, encephalopathy, encephalitis, stroke, Guillain-Barré syndrome, benign intracranial hypertension, meningoencephalitis, ADEM, impairment of cranial nerves, transverse myelitis, fatal cerebral edema, vision changes, neuritis, labyrinthitis, myositis, status epilepticus, coma, paresthesia, dysautonomia, demyelinating disease, cerebellar ataxia, axial hypotonia, peripheral neuropathy, and others (Table 2). On epilepsy, in particular, a comparative study was carried out (Annex 1).

As for comorbidities and their relationship with the neurological condition, further investigation is still needed, mainly because children have fewer comorbidities than the adult population. However, evidence points to a greater risk of developing complications in children with associated comorbidities[14,17], mainly for the development of status epilepticus in children with a history of neurological disorders[13].

Regarding the radiological alterations found, it is important to highlight the findings in the splenium of the corpus callosum, which is an important site of injury in children with neurological manifestations[6,9,17]. In addition, lesions in the thalamic nucleus and cerebral and intramyelin edema were also found[6,9,17]. In cases of vascular accidents, lesions were found in multiple territories, including occlusion of large vessels[16].

The analysis of cerebrospinal fluid in the patients studied also points to an interesting result. Most cases had a negative culture for SARS-CoV-2 in the cerebrospinal fluid[5,9,15,17]. Only one study was culture positive[18]. However, other CSF alterations, such as the presence of inflammatory markers, were found in more patients, although rare[17]. It is worth mentioning that the collection and analysis of cerebrospinal fluid are not performed in all cases, which may impact the results found.

Another extremely relevant data found in this review concerns the prognosis of children. In general, children have a good prognosis[6], in which most cases present full recovery or minimal neurological sequelae[10]. Furthermore, the younger the patient, there tends to be a better prognosis and survival[12]. However, children diagnosed with co-infection are more severe cases and have higher mortality. In one study, all patients with another associated infection died[10].

Some analyzed articles also addressed pathophysiological hypotheses for the involvement of the central nervous system by SARS-CoV-2 infection. Two main mechanisms were identified: direct neuroinvasion and the secondary inflammatory response associated with activation of the immune system[3,9,15,17,18]. Other hypotheses raised were: indirect effects of cardiovascular complications and hypoxia, invasion via leukocytes and endothelium and damage to the blood-brain barrier.

Finally, all articles point to the need for further studies on the subject and the impact of these neurological manifestations on the development of affected children. Another question is about the understanding and confirmation of the relationship between the nervous system changes and the COVID-19 condition, seeing as necessary to confirm the existence of this relationship[3,16].

CONCLUSIONS

The present work allows us to conclude that neurological manifestations are an important aspect of the course of COVID-19 in the pediatric population and therefore deserve clinical attention. Thus, its undergraduate study is extremely important and relevant, and the clinical cases created in this project are a form of application in this context.

In addition, the literature review carried out allows us to conclude that, given the importance of the topic, it is necessary to carry out more research, both on the manifestations themselves and on their impact on long-term development. Another point of fundamental investigation is how these manifestations actually relate to the COVID-19 situation.

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Annex 1 - Epilepsy comparative study

From the analysis of 6 articles on neurological manifestations of COVID-19 in the pediatric population, it was possible to observe that epilepsy is an important manifestation in this context - only one article did not mention epileptic seizures as a manifestation. According to data from the NewYork-Presbyterian Morgan Stanley Children's Hospital, of the 35 children analyzed with neurological impairment by COVID-19, 4 (11%) had epileptic seizures[1]. In another study, of 3,707 pediatric patients with COVID-19 analyzed, 42 had specific neurological manifestations, such as epileptic seizures, presented by 12 patients, who were with severe or critical illness[2]. Of these cases, all had symptomatic acute seizures and occurred during febrile episodes, with only one case of status epilepticus, and all patients survived. Another incidence found for seizures in pediatric patients with COVID-19 was 14 out of 60 cases [3]. One hypothesis to explain this situation is the pro-inflammatory state caused by the storm of cytokines (IL-1, IL-6, TNFa and IL-17), which cross the blood-brain barrier leading to neuroinflammation and consequent state of neuronal hyperexcitation[1].

Although different studies point to epilepsy as a relevant neurological manifestation associated with SARS-CoV-2 infection in children, different epidemiological data were found, requiring more specific studies regarding this complication. While one study consider seizures as a rare neurological manifestation of COVID-19[2], another points out as one of the main ones[3]. However, it is worth mentioning that the first was published in 2020 and the second, in 2021, a significant time interval that must be considered, since the context of the object of study is a pandemic that is still ongoing. Thus, the need for research on the subject over time becomes even more evident, in order to reach more concrete results on the subject.

Of the articles analyzed, 21 clinical cases were described that had a seizure, removing the duplication found in the review article by Siracusa et al.[3] – in which there is a description of the same cases of Raj et al.[4]. These cases are summarized below:

Reference	Case resume
Lindan et al.[5]	2 months, without comorbidities, fever, cough and convulsion. Use of supportive therapy and administration of antiepileptic drugs. Normal to discharge, 8 days after presentation.
	1 year and 2 months, without comorbidities, fever, encephalopathy, dystonic posture and seizure. Patient intubated and using supportive therapy, administration of anti-epileptic drug was performed. Normal to discharge, 1 month after presentation.
	9 years old, autistic, with fever, cough, headache, encephalopathy, photophobia, phonophobia and convulsion. Patient intubated and using supportive therapy, performed intravenous immunoglobulin. Normal to discharge 5 weeks after presentation.
	5 years, no comorbidities, fever, headache, seizure. Tuberculosis co-infection, showed thromboembolic pattern and myelitis. Use of supportive therapy, with intubation, performed suboccipital craniectomy with cerebellar biopsy. Death one month after presentation.
	15 years old, pregnant, fever, convulsion and hypertension with respiratory symptoms. Patient with supportive therapy. Normal to discharge 2 weeks after presentation.
	14 years old, no comorbidities, fever, encephalopathy, convulsion, respiratory failure due to aspiration. Patient intubated and with supportive therapy, performed numerous immunomodulatory therapies.
	4 years and 2 months, no comorbidities, seizure, facial paralysis, four-limb dysfunction, rash. High dose steroid use. Improvement after 2.5 months of presentation, with mild cerebellar ataxia.
Panda et al.[2]	6 weeks, brief episodes of tonic seizures, with normal neuroimaging and cerebrospinal fluid analysis
Raj et al.[4]	2 years old, had status epilepticus (other symptoms: watery stools, abdominal pain, hypotensive shock and hypoxia). Diagnosed with acute febrile encephalopathy. After medication and improvement of the condition, he had no more seizures.
	15 months, presented with simple febrile seizures, diagnosed with SIM-C with Kawasaki phenotype. Improvement after medication and improvement of the condition.
	8 months, with high fever for one day, presented the first episode of generalized tonic-clonic seizure lasting 20 minutes. Medicated with midazolam initially and levetiracetam due to prolonged episode. No other symptoms. On the third day, he no longer had a fever, and was discharged with a prescription for levetiracetam with the diagnosis of febrile status epilepticus.
Siracusa et al.[3]	11 years old, had only epileptic seizures as symptoms, without respiratory symptoms or fever. There was no diagnosis of SIM-C and normal CT. Full recovery.
	2 years and 9 months, with epileptic seizures, altered mental status and dysarthria, without respiratory symptoms, but with fever. MRI indicated right occipital mass and intracerebral hemorrhage. EEG: generalized deceleration (mass pathology: normal brain tissue with dilated vessels and hemorrhage). Full recovery.
	14 years old, epileptic seizures and central apnea, with respiratory symptoms, fever, nasal congestion and myalgia. EEG: epileptiform abnormalities. It showed improvement.
	11 years old, seizures and fever. EEG: Intermittent frontal delta activity. Full recovery.
	12 years, convulsions, dysarthria and hemiparesis. MRI: acute infarction with left cerebral artery narrowing. Improvement and under rehabilitation.
	2 months, seizures and headache. No neuroimaging changes. Full recovery.
	13 years old, seizures, headache, irritability and fever. No neuroimaging changes. Full recovery.
	3 years, convulsions, fever and hypotension. Diagnosis of SIM-C. CT: cerebral edema. MRI: intracerebral hemorrhage in the right occipital lobe. Full recovery.
	12 years, seizure, fever, rash, conjunctivitis, neck swelling, hypotension. Diagnosis of SIM-C. EEG: focal epilepsy with an increase in the central region. Full recovery.
	9 years old, convulsion, fever and vomiting. EEG: delta activity in the right hemisphere. Full recovery.
	17 years old, seizure, fever, respiratory symptoms. Diagnosis of SIM-C. MRI: multifocal cortical, cerebellar, and thalamic swelling. EEG: lateralized independent bilateral periodic epileptiform discharges.

In view of this context, epilepsy should be a point of attention in the management of pediatric patients with COVID-19 and an object of study for a better understanding of the condition associated with SARS-CoV-2 infection.

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