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ORIGINAL ARTICLE

Neurological manifestations temporally associated with SARS-CoV-2 infection in pediatric patients in Mexico

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Abstract

Purpose To describe the temporal association of specific acute neurological symptoms in pediatric patients with confirmed SARS-CoV-2 infection between May and August 2020.

Methods We performed a recollection of all the clinical and laboratory data of patients having acute neurological symptoms temporally associated with SARS-CoV-2 infection at a third-level referral hospital in Mexico City (Instituto Nacional de Pediatría). Patients in an age group of 0–17 years with acute neurological signs (including ascending weakness with areflexia, diminished visual acuity, encephalopathy, ataxia, stroke, or weakness with plasma creatinine kinase (CK) elevation) were evaluated.

Results Out of 23 patients with neurological manifestations, 10 (43%) had a confirmed SARS-CoV-2 infection. Among the infected patients, 5 (50%) were males aged 2–16 years old (median age 11.8 years old). Four (40%) patients confirmed a close contact with a relative positive for SARS-CoV-2, while 6 (60%) cases had a history of SARS-CoV-2–related symptoms over the previous 2 weeks. The following diagnoses were established: 3 cases of GBS, 2 of ON, 2 of AIS, one of myositis with rhabdomyolysis, one ACA, and one of anti-NMDA-R encephalitis.

Conclusions Neurological manifestations temporally associated with SARS-CoV-2 infection were noticed in the pediatric population even without respiratory symptoms. In this study, 2 of 6 symptomatic patients had mild respiratory symptoms and 4 had unspecific symptoms. During this pandemic, SARS-CoV-2 infection should be considered as etiology in patients with acute neurological symptoms, with or without previous respiratory manifestations, particularly in teenagers.

Keywords SARS-CoV-2 · Optic neuritis · Guillain-Barré syndrome · Anti-NMDA-R encephalitis · Acute ischemic stroke · Acute cerebellar ataxia · Children

Introduction

The emergence of the COVID-19 pandemic [1], caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to be a challenge to physicians worldwide. Many SARS-CoV-2 confirmed cases have neurological symptoms and complications caused by either direct infection of the central nervous system or inflammatory

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or autoimmune mechanisms, which can develop during or after the viremia [2].

Information about the clinical status of COVID-19 in children is continuously growing. Previous systematic reviews have shown that SARS-CoV-2 infection in this group of age has a particular clinical course with milder respiratory manifestations, with the possibility of developing a systemic disease [3, 4].

Neurological symptoms associated with SARS-CoV-2 are increasingly recognized. In a case series of 27 children with COVID-19, 4 (14.8%) patients had either encephalopathy, headache, brainstem and cerebellar signs, muscle weakness, or reduced reflexes [5]. A more recent multinational case-series of 38 children with disorders related to the central nervous system (CNS) reports encephalomyelitis-like changes, myelitis, and cranial nerve enhancement [6]. This manuscript aims to further investigate pediatric patients with acute neurological symptoms and positive for anti-SARS-CoV-2 antibodies.

Methods

We analyzed 23 patients reporting neurological symptoms who arrived, between May and August 2020, at the emergency room of the Instituto Nacional de Pediatría (INP), which is a third-level referral pediatric hospital in Mexico City. Clinical and neurological evaluations were conducted, followed by contact tracing details for COVID-19 disease. We classified those patients who met clinical criteria for suspected SARS-CoV-2 infection [7] (Table 1). All patients were hospitalized due to neurological symptoms.

After the initial approach, 12 (52%) patients underwent polymerase chain reaction (PCR) testing for SARS-CoV-2 (N, E, and RdRP genes) detection in nasal samples. Both IgG and IgM anti-SARS-CoV-2 antibodies were quantified in the serum of all 23 patients. In 15 (21%) patients, the cerebrospinal fluid (CSF) was analyzed for anti-SARS-CoV-2 antibodies and a PCR test was done in the CSF of one patient as well. Thirteen patients were excluded from further examination due to negative results for SARS-CoV-2 infection.

Table 1 CONAVE criteria for suspected and confirmed cases of COVID-19 effective in Mexico [7]

Suspected case	Person of any age who, in the last 7 days, has presented at least two of the following signs or symptoms: cough, fever, and headache. Accompanied by at least one of the following signs or symptoms: dyspnea, arthralgia, myalgia, odynophagia, rhinorrhea, conjunctivitis, or chest pain.
Confirmed case	Person who meets the operational definition of a suspected case and has a confirmed diagnosis by the national network of public health laboratories recognized by the InDRE

InDRE, Institute for Epidemiological Diagnosis and Reference "Dr. Manuel Martínez Báez"

CONAVE, Comité Nacional de Vigilancia Epidemiológica (National Committee of Epidemiological Vigilance)

For Guillain-Barré syndrome (GBS), patients underwent nerve conduction studies (NCS) and lumbar puncture (LP) for CSF analysis. Optic neuritis (ON) patients underwent brain and spine magnetic resonance imaging (MRI), LP for CSF analysis, and anti-aquaporin-4 (AQP4) antibody quantification. Acute ischemic stroke (AIS) was evaluated by non-contrast computer tomography (NCCT) followed by MRI. Myositis was assessed and monitored by creatinine kinase (CK) serum level quantification. The patient with anti-NMDA-R encephalitis underwent MRI and LP for CSF analysis, including CSF anti-NMDA-R autoantibody (GluN1 subunit) quantification. Acute cerebellar ataxia (ACA) was evaluated by NCCT and LP for CSF analysis. All CSF evaluations included routine PCR analysis for *E. coli*, *H. influenzae*, *L. monocytogenes*, *N. meningitides*, *S. agalactiae*, *S. pneumoniae*, *CMV*, *Enterovirus*, *HSV 1 & 2*, *Parechovirus*, *VZV*, *Herpesvirus 6 and 7*, and *Cryptococcus.*

A semi-qualitative test on an automated platform (VIDAS® Biomerieux) was used for anti-SARS-CoV-2 antibody assessment. The sandwich-type immuno-enzymatic method revealed the presence of IgG or IgM by fluorescence emission (FIA = fluorescent Immunoassay). The solid phase was attached to the recombinant antigen of the nucleocapsid of SARS-CoV2. The IgG (IgM) component of the sample was captured in the fixed antigen, followed by an anti-IgG (anti-IgM) conjugate labeled with alkaline phosphatase, which bound the IgG (IgM) of the subject. The presence of anti-SARS-CoV2 antibodies was detected by the hydrolysis of the 4-methyl-umbelliferyl-phosphate compound, generating a 4-methyl-umbelliferone compound, which emitted fluorescent light measured at a wavelength of 450nm. The fluorescence intensity is directly proportional to the level of the antibodies present in the sample. The results are shown with a cut-off index (COI) of 1.0.

Results

We analyzed 10 consecutive cases of patients with acute neurological manifestations along with confirmed SARS-CoV-2 infection, representing 43% of the original sample. Sex distribution was 1:1. Ages ranged from 2 to 16 years old, with a mean age of 11.8 years. The time between the onset of neurological symptoms and clinical evaluation varied from some hours to up to 2 weeks. The following diagnoses were established: 3 patients had GBS, 2 patients had ON, 2 patients had AIS, one patient had myositis with rhabdomyolysis, one

patient had ACA, and one patient had anti-NMDA-R encephalitis.

Two patients had positive nasal swabs for SARS-CoV-2 PCR test, one patient tested positive only for serum IgM antibodies, 4 patients tested positive for both serum IgM and IgG antibodies, and 2 patients tested positive only for serum IgG. The patient with anti-NMDA-R encephalitis had SARS-CoV-2 antibodies (IgG) and a positive PCR test positive in CSF, but not in serum. Further results are described in Table 2.

According to the provisional case definitions proposed by Ellul et al. [8], one patient met the criteria for confirmed SARS-CoV-2 (evidence for SARS-CoV-2 in CNS), 3 cases had probable disease (lack of evidence of other commonly associated causes), and 4 had possible disease (evidence of other commonly related causes, such as cardiovascular risk) (Table 3).

To establish a temporal relation between SARS-CoV-2 infection and neurological diseases, we analyzed the incidence of the conditions mentioned above in the same time frame in 2019 (Table 4).

Discussion

As the number of cases of SARS-CoV-2 infection continues to grow, the knowledge about the characteristics of this novel disease continues to increase. Previous beta coronaviruses (MERS-CoV, SARS-CoV-1, NCoV-OC43, and HCoV-HKU1) frequently invade the CNS in addition to the respiratory tract [9]. There are different theories regarding the pathophysiology of the CNS invasion: transmission through the olfactory nerve in a similar way to SARS-CoV-2, even in the absence of the virus in other tissues such as lungs, blood-brain barrier crossing, and infiltration of infected immune cells (types 2 and 3 of innate lymphoid cells) [9]. Infection is thought to take place through different receptors, including ACE2, BSG, and NRP1 [10]. Several cells such as neurons and glial cells located in different brain areas express ACE2, particularly in the brainstem, the subfornical organ, the paraventricular nucleus, the nucleus of the tractus solitarius, and the rostral ventrolateral medulla. In addition, there is suspected dysregulated systemic immune response with hyperactivity of innate immunity, a massive release of cytokines and other inflammation signals [7, 9] followed by immunosuppression[10]. Pathophysiological mechanisms such as molecular mimicry, bystander activation and damage, persistent immune activation, and netosis (the formation of neutrophil extracellular traps, NETs) can give rise to autoimmunity [11]. SARS-CoV-2 might also affect oligodendrocyte differentiation due to ACE2 expression on oligodendrocyte progenitor cells, consequently slowing recovery in demyelinating diseases [10, 12]. A full description of these mechanisms is continuously evolving, and new information is now becoming available.

This article reports a series of 10 patients with a mean age of 11.8 years old, in which 8 of them were adolescents, reflecting the fact that infants and young children are less severely affected by SARS-CoV-2 infection and its related disorders, with the exception of Kawasaki-like syndrome, and thus, may have a lower incidence of neurological symptoms related to COVID-19.

GBS is one of the most reported neurological, post-infection diseases associated with COVID-19, even in the child population [13, 14]. There is evidence for a slight prevalence of acute inflammatory demyelinating polyneuropathy (AIDP) over acute motor axonal neuropathy (AMAN), and post-infection cases seem to predominate over para-infection cases [15]. Additionally, there have been reports of adult patients having GBS weeks after being confirmed as asymptomatic carriers [16]. It is still unclear if SARS-CoV-2 induces the production of specific anti-ganglioside antibodies usually associated with GBS [17]. The 3 patients diagnosed with GBS were in their late childhood or adolescence and had an AIDP pattern in the nerve conduction studies. Two were recurring cases, as they have had a similar ailment in a prior period of 4 months to 3 years. Due to the characteristics of the episodes, we excluded the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy. Moreover, the patients recovered the ability to walk and run independently. To our knowledge, this has not been reported, and specific pathophysiology has not been established yet. We cannot assure that GBS recurrence in these cases has a causal relationship to SARS-CoV-2 infection.

ON is a manifestation of acute demyelinating disease involving the optic nerve and has been previously associated with viral infections and other autoimmune diseases [18]. Feline and murine models of the disease have reported ON as a possible manifestation of COVID-19 [19]. Recently, there have been isolated reports of ON pathology in confirmed SARS-CoV-2-infected adults [20, 21]. To our knowledge, this is the first report of pediatric patients having ON associated with SARS-CoV-2 infection. Both cases were teenagers. The MRI showed optic nerve hyperintensities in the short tau inversion-recovery (STIR) sequence and therefore ruled-out other possible etiologies. The patients recovered entirely and further monitoring is provided in case they show other demyelinating signs. There is a report of cranial nerve enhancement in 13 children, in which some of them lack of the corresponding neurological symptoms [6].

Cases of AIS and cerebral venous sinus thrombosis (CVST) had been reported in adult patients with COVID-19 [22]. AIS is attributed to an inflammatory or hypercoagulable condition induced by SARS-CoV-2 infection [23], especially in cases with increased cardiovascular risks (hypertension, diabetes, cardiomyopathy), where thromboembolic

Table 2 Clinical and laboratory findings in patients positive for SARS-CoV-2

Patient	Age	Gender	Medical history	SARS-CoV-2 contact	COVID 19 symptoms	Neurological clinical manifestations	Complimentary studies	Diagnosis	SARS-CoV2 PCR	Serum SARS-CoV-2 IgM¤	Serum SARS-CoV-2 IgG¤	CSF	CSF antibodies SARS-CoV-2 IgG¤	Outcome
1	9	Male	GBS at 6 years old	Yes	None	Pain in lower limbs, ascendant weakness, hypotonia, diminished MSR in lower limbs.	NCS: AIDP	Guillain-Barré syndrome	Negative	Negative	Positive (56.2)	Proteins: 129.4 Cells: 0	Negative	Hughes scale: 0
2	14	Male	PH±	No	Fever, rhinorrhea	Paresthesia in feet, ascendant weakness, hypotonia, diminished MSR in lower limbs.	NCS: AIDP	Guillain-Barré syndrome	Not performed	Positive (34.9)	Positive(4.81)	Proteins: 202 Cells: 0	Negative	Hughes scale: 0
3	12	Female	GBS 4 months earlier (12 years old)	Yes	None	Dysphonia, hypotonia, ascendant weakness, diminished MSR in upper limbs, and absent MSR in lower limbs.	NCS: AIDP	Guillain-Barré syndrome	Not performed	Negative	Positive (23.76)	Proteins: 237.4 Cells: 0	Negative	Hughes scale: 0
4	15	Female	PH±	Yes	Fever, headache, vomits	Diplopia, bilateral ocular pain, and diminished visual acuity, left VI cranial nerve paresis.	MRI: optic nerve hyperintensities	Bilateral optic neuritis, left VI cranial nerve paresis	Negative	Negative	Positive (72.8)	Proteins: 24 Cells: 0	Negative	Visual acuity fully recovered No evidence of other demyelinating disease
5	14	Female	PH±	Yes	Headache, myalgias, arthralgias	Headache, left ocular pain, diminished visual acuity of left eye.	MRI: left optic nerve hyperintensity	Left optic neuritis	Not performed	Positive (21.62)	Positive (1.34)	Proteins: 21.4 Cells: 0	Negative	Visual acuity fully recovered No evidence of other demyelinating disease
6	14	Male	PH±	No	None	Altered behavior and mental status, seizures, insomnia, orolingual dyskinesias	Positive anti-NMDA-R antibodies in CSF.	Anti NMDA encephalitis	*Positive in CSF*	Negative	Negative	Proteins: 23 Cells: 2	Positive (5.9)	Rankin Score: 0, absolute control of epilepsy, presence of psychiatric symptoms
7	12	Male	Aortic coarctation*	No	None	Altered mental status, aphasia, seizures, left hemiparesis.	MRI: AIS in left frontal lobe.	Ischemic stroke§	Not performed	Negative	Positive (41.79)	Not performed	Not performed	Dysphasia, hemicorporeal weakness, acalculia
8	16	Female	Acute myeloblastic	No	Fever	Irritability, left hemiparesis, weakness, and mixed aphasia.	MRI: AIS in watershed areas	Ischemic stroke	Not performed	Positive (8.55)	Negative	Proteins: 32 Cells: 0	Not performed	Deceased (cause: bacterial sepsis)

Table 2 (continued)

Patient	Age	Gender	Medical history	SARS-CoV-2 contact	COVID 19 symptoms	Neurological clinical manifestations	Complimentary studies	Diagnosis	SARS-CoV2 PCR	Serum SARS-CoV-2 IgM¤	Serum SARS-CoV-2 IgG¤	CSF	CSF antibodies SARS-CoV-2 IgG¤	Outcome
			leukemia M2											
9	10	Female	PH±	No	Fever, myalgias	Rhabdomyolysis, gait abnormalities.		Myositis	Positive	Negative	Negative	Not performed	Not performed	Asymptomatic
10	2	Male	PH±	No	Fever, rhinorrhea, irritability, cough	Ataxia	NCCT: normal	Para infectious ataxia	Positive	Positive (223)	Positive (39.5)	Proteins: 89 Cells: 6	Negative	Asymptomatic

*Diagnosed after the ischemic stroke

¤ Semi-quantitative test, positive ≥ 1.0

CFS, cerebrospinal fluid

PH±, previously healthy

Table 3 Classification of cases as confirmed, probable, or possible association with SARS-CoV-2 infection

Patient	Diagnosis	SARS-CoV-2 CNS sample	Evidence of other commonly associated causes	Provisional case definitions for the association of COVID-19 with neurological disease [8]
1	Guillain-Barré syndrome	Negative	Negative infectious CSF PCR panel, negative ***C jejuni*** PCR	Probable
2	Guillain-Barré syndrome	Negative	Negative infectious CSF PCR panel	Possible
3	Guillain-Barré syndrome	Negative	Negative infectious CSF PCR panel	Possible
4	Bilateral optic neuritis, left VI cranial nerve paresis	Negative	Negative infectious CSF PCR panel	Probable
5	Left optic neuritis	Negative	Negative infectious CSF PCR panel	Probable
6	Anti NMDA encephalitis	Positive	Negative infectious CSF PCR panel	Confirmed encephalitis
7	Ischemic stroke	Not performed	Aortic coarctation	Possible
8	Ischemic stroke	Not performed	Acute myeloid leukemia	Possible
9	Myositis	Not performed	Negative respiratory panel	Probable
10	Para infectious ataxia	Negative	Negative infectious CSF PCR panel	Probable

mechanisms may be facilitated [24]. One of the patients described here have had a previously undiagnosed aortic coarctation with severe arterial hypertension in the upper extremities but had no other pro-thrombotic risk factors. The MRI revealed several noncontiguous ischemic lesions in the left middle cerebral artery (MCA) territory, suggesting an embolic mechanism. This patient persisted with right hemiparesis and expression dysphasia at hospital discharge, but 1 month later, both symptoms had improved. The other AIS patient, an adolescent, had M2 acute myeloid leukemia and was hospitalized for acute altered state of consciousness and fever, which was later related to SARS-CoV-2 infection. This patient passed away a few weeks later due to complications from bacterial sepsis. The multinational report previously mentioned [6] also describes 4 children with thromboischemic disease, and 3 of those had co-infections.

Increased creatinine kinase levels are a common finding in COVID-19 confirmed patients [25], which can be attributed to primary viral myositis or by myopathy secondary to critical illness [8]. Rhabdomyolysis has also been reported in the pediatric population [26]. Our patient having acute myositis showed a simultaneous respiratory disease. She had a full recovery.

Table 4 Comparative number of total cases for the months of May–August (2019 and 2020)

Disease	2019	2020	Year-over-year increase
Guillain-Barré syndrome	4	11	2.7
Anti-NMDA-R encephalitis	2	5	2.5
Optic neuritis	2	3	1.5
Acute ischemic stroke	0	2	NA
Acute cerebellar ataxia	0	1	NA
Myositis with rhabdomyolysis	0	1	NA

Anti-NMDA-R encephalitis has previously been associated with SARS-CoV-2 infection in adults [27]. Our 14-year-old patient developed subacute encephalitis with antibodies to both NMDA-R and SARS-CoV-2 in CSF, and a positive SARS-CoV-2 PCR test in CSF as well. These findings are suggestive of intrathecal synthesis of these antibodies. Since Anti-NMDA-R encephalitis is also associated with HSV infection in the CNS, it is possible that SARS-CoV-2 disease induces autoimmune encephalitis due to production of anti-NMDA-R or other, not well defined, auto-antibodies. The patient received intravenous methylprednisolone and immunoglobulin treatment and had a partial recovery of the neurological symptoms.

The infant with acute cerebellar ataxia had a full recovery. The physiopathology might be similar to those viral infections related to acute cerebellar ataxia.

Overall, the outcome was similar to that expected of the natural history of the disease, without the necessity of a different management approach, in contrast to the possible appearance of chronic symptomatology reported in adult patients. Since the blood-brain barrier deteriorates with age, it is possible that adults become more susceptible to neuroinvasion during SARS-CoV-2 infection and thus, long-term consequences are triggered, such as demyelination, neurodegenerative changes, and senescence of several different CNS cell types, perpetuating a neuroinflammatory state [12]. Other hypotheses for these differences between children and adults include lesser ACE2 expression on children's respiratory tract [9] and routine childhood vaccination [28].

The frequency of neurological diseases was overestimated throughout the rest of the year 2020, and especially in comparison with the incidence of these disorders in 2019 and 2018. We did not assess the rest of the patients for SARS-CoV-2

infection; therefore, although suggestive, it cannot be considered that neurological manifestations were caused by SARS-CoV-2.

Conclusions

Reporting case series like the present work is essential because SARS-CoV-2 infection is a major global health issue that can be temporally associated with neurological symptoms, even in the absence of acute respiratory illness. The experience in pediatric populations is scarce but increasingly growing. The main findings in this series include a higher number of cases in older children and adolescents, with GBS as the most common condition associated with SARS-CoV-2 infection among other inflammatory and demyelinating diseases temporally associated with SARS-CoV-2 infection as well. According to the data presented, we may assume that SARS-CoV-2 infection has increased the incidence of neurological symptoms in pediatric patients treated in this third-level referral center, even in the absence of respiratory manifestations (Table 4). However, not all acute neurological symptoms were related to SARS-CoV-2 infection. Still, in the current pandemic context, it is paramount to consider this as a possibility to initiate appropriate clinical approaches and treatment while protecting health-care workers and families from virus exposure.

Awareness of possible association with SARS-CoV-2 infection as a trigger for acute neurological diseases highlights the need for an appropriate epidemiological and serologic evaluation in the presence of neurological diseases. At the moment, we are performing COVID-19 tests for all patients with acute neurological symptoms.

The authors recommended worldwide further investigation in this area to understand a concluding correlation between COVID-19 and neurological manifestations. This could further support the conclusions reported in this work about the Mexican population. In this way, the physicians can review if there is a need to change the clinical response to the standard treatment procedure of patients having COVID-19 to minimize the neurological damage.

Abbreviations *SARS-CoV-2,* Severe acute respiratory syndrome coronavirus 2; *CK,* Creatinine kinase; *ON,* Optic neuritis; *GBS,* Guillain-Barré syndrome; *AIS,* Acute ischemic stroke; *NMDA-R,* N-methyl-D-aspartate receptor; *PCR,* Polymerase chain reaction; *NCS,* Nerve conduction studies; *LP,* Lumbar puncture; *CSF,* Cerebrospinal fluid; *MRI,* Magnetic resonance imaging; *AQP-4,* Aquaporin-4; *NCCT,* Non-contrast computer tomography; *CSVT,* Cerebral venous sinus thrombosis; *AMAN,* Acute motor axonal neuropathy; *AIDP,* Acute immune demyelinating neuropathy; *CONAVE,* Comité Nacional de Vigilancia Epidemiológica

Declarations

Conflict of interest None

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