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Pediatrics COVID-19 and neurological manifestations: Single tertiary centre experience

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ABSTRACT

Importance: Coronavirus disease 2019 (COVID-19) is a severe acute respiratory syndrome that is caused by a novel coronavirus 2 (SARS-CoV-2). It originated in China late December 2019 and was declared a global pandemic on March 12, 2020. Most reports of COVID-19 cases either presented with neurological manifestations or complications involve adults. Only few cases were reported in pediatric patients

Objective: To report COVID-19 pediatric cases with neurological manifestations and identify the wide spectrum of its manifestations.

Design, setting, and participants: This was a retrospective, observational case series. Data of pediatric patients infected by SARS-CoV-2 presenting with neurological manifestations at King Abdullah Specialized Children Hospital in King Abdulaziz Medical City in Riyadh were collected from May 23 to June 30, 2020.

Results: We encountered 5 COVID-19 cases with neurological manifestations. Three patients who were previously healthy had new-onset neurological symptoms. Symptoms and signs included encephalopathy, ataxia, headache, seizure, papilledema, ophthalmoplegia, hyporeflexia, and different clinical spectra, such as Miller Fisher syndrome, meningoencephalitis, and idiopathic intracranial hypertension. Other patients attending our center were incidentally found to be SARS-CoV-2-positive, which caused a delay in the investigations required to reach diagnosis.

Conclusions and relevance: Our cases highlight the wide clinical spectrum of neurological manifestations in COVID-19 patients. Given the paucity of information about pediatric COVID-19 cases with neurological symptoms, we here reported these cases to shed light on the association between SARS-CoV-2 and neurological presentation. Moreover, our study indicates that many investigations are being delayed and could affect diagnosis and treatment.

1. Introduction

Coronavirus disease 2019 (COVID-19), which was first recognized in December 2019, and reported in Wuhan, China, is caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was declared "a public health emergency of international concern" by World Health Organization (WHO) on January 30, 2020, and "a global pandemic" on March 12, 2020. The number of cases continues to increase, and as of June 22, 2020, approximately 8.8 million confirmed cases have been reported worldwide, with more than

Abbreviations: COVID-19, coronavirus disease 2019; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; ER, emergency room; IVIG, intravenously administered immunoglobulin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MCA, middle cerebral artery; MRI, magnetic resonance imaging; NICU, neonatal intensive care unit; WBC, white blood cell.

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200 countries affected globally, while there are approximately 150,000 confirmed cases in Saudi Arabia [1].

Respiratory symptoms are the primary presentation of this virus, which primarily targets the human respiratory system. In addition, some patients also developed non-specific neurological symptoms, including headache, anosmia, dysgeusia, dizziness, disturbed consciousness, and paresthesia. However, over time, increasing numbers of adult patients with COVID-19 began to present with neurological manifestations, such as acute cerebrovascular disease, encephalitis, seizure, Guillain-Barré syndrome, and Miller Fisher syndrome [2–4].

During this pandemic, data regarding the percentage of children infected with COVID-19 has varied among countries. Latest data from the USA has shown that 1.7% of children aged <18 years are affected [5]; according to available literature, most of these pediatric cases presented with mild symptoms, and some were asymptomatic and were identified by routine screening. The majority of published COVID-19 cases with neurological manifestations are adults. Only two pediatric cases had been reported in literature; one case involved a 6-week-old, previously healthy baby presenting with seizure and fever [6]. The other case was of a 12-year-old-boy with a new onset seizure, right-sided hemiparesis, and dysarthria with radiological evidence of acute infarction, along with focal irregular narrowing and banding of the left middle cerebral artery (MCA) of the proximal M1 segment [7]. Recently, there have been reports of children with COVID-19 pediatric multisystem inflammatory syndrome, who had neurological symptoms [8,9].

Upon re-evaluating the literature on previous epidemics of Middle East respiratory syndrome coronavirus and SARS-CoV, we found that, although rare, there were cases with neurological manifestations similar to those being observed in the current COVID-19 pandemic. These cases have spurred studies of the mechanism and pathophysiology of the association between this virus and the CNS in order to shed light on the neuropathogenic effect or neuroinvasive capabilities of the virus [10]. Consequently, we here describe our experience of six pediatric COVID-19 cases presenting with different neurological manifestations.

2. Methods

Here we report six patients who presented to our hospital with different neurological manifestations. They were all confirmed to have COVID-19 positive. All clinical, radiological and laboratory investigations are collected. All data gathered were collected in retrospect using our electronic medical records. This also includes their outcome to the best of our knowledge.

3. Results

3.1. Case 1

A 9-year-old, previously healthy boy presented with dysarthria and gait instability noted since wake up this am. Two days prior to that he complained of mild headache that responded to simple analgesia.

On exam, he was able to follow commands with intact comprehension, and demonstrated fluent hypophonic speech. Cranial nerve examination was normal, except for a mild lateral gaze limitation bilaterally, other extraocular movements were intact. There was normal tone and power in all extremities, with normal reflexes throughout and a flexor plantar reflex bilaterally. His sensory examination was normal. Cerebellar examination showed mild appendicular dysmetria with overshooting. His gait was wide-based, with an abnormal tandem gait. Brain computed tomography (CT) with angiogram was non-revealing. Baseline laboratory examinations in the ER were all normal, including complete blood count, electrolytes, creatine phosphokinase, renal and liver function tests.

On the second day after admission, he developed dysphagia with difficulty on swallowing liquid; on that day, the result of his nasopharyngeal swab test for COVID-19, which is a standard precaution for any new admission at our center during this pandemic, conducted by qualitative real-time reverse-transcriptase–polymerase chain reaction (PCR) assay, was positive. Lumbar puncture was attempted but was not successful.

Four days after presentation, he complained of diplopia, and upon re-examination, he was noted to have bilateral ptosis with worsening of his extraocular movements. He exhibited external ophthalmoplegia with severe limitation of extraocular movements in all directions, with a normal pupillary response to light, and without a relative afferent pupillary defect. He then had diminished reflexes in the upper and lower limbs. At that point a provisional diagnosis of Guillain Barré syndrome variant was suspected and was treated with intravenously administered immunoglobulin (IVIG) 2 g/kg over a period of 5 days. Magnetic resonance imaging (MRI) of his brain and spine with contrast showed thickening and enhancement of the nerve roots of the cauda equina and conus medullaris, with no acute intracranial pathology (Fig. 1). Nerve conduction studies were not done due to the current COVID-19 pandemic situation. Diagnosis of Miller Fisher syndrome was later confirmed by positive ganglioside antibodies in the serum, specifically GQ1b (IgM and IgG) antibodies.

On the third day of starting IVIG, he showed improvement of dysphagia and diplopia. His extraocular movements, ptosis, and ataxia improved significantly over the subsequent days and he began to mobilize without assistance. He was discharged approximately 2 weeks after admission. Two weeks after discharge, the patient had mild ataxic gait with normal extraocular movements.

3.2. Case 2

A 6-year-old, previously healthy boy presented to the ER with second time generalized convulsion. He had similar event one weak earlier associated with fever. Fever persisted since then and was treated with antibiotic in a local hospital.

Upon presentation He was awake, alert, oriented, and following commands. The rest of neurological exam was unremarkable.

A full sepsis work-up was performed. The patient had leukocytosis of 16.9×10^3, with predominant neutrophils. Urinalysis was normal, without suggestions of urinary tract infection. Blood and urine culture were negative. CSF analysis showed a white blood cell (WBC) count of 12, with normal protein and glucose levels, and was negative for culture and a CSF viral panel. The nasal swab of COVID-19 was positive, but CSF COVID-19 PCR was negative. The patient was admitted as a case of partially treated meningitis, and was started on vancomycin and ceftriaxone. Based on the history of two prolonged seizures, the Pediatric Neurology service was involved and he was started on valproic acid. The patient completed a 5 days' course of antibiotics, after which he was doing well and vitally stable, with no more seizures. He was thus discharged home in a stable condition.

3.3. Case 3

A 10-year-old, previously healthy girl presented to the ophthalmology clinic as she was complaining of eye dryness and a recurring headache lasting 2 months. She also complained of difficulties closing her eyes fully while sleeping. Examination showed bilateral papilledema, with tortious blood vessels and disc hyperemia, and elevated optics disc. A B-scan ocular ultrasound was done and showed no evidence of drusen body.

She was immediately referred to ER to be seen by a pediatric neurologist. A brain CT was performed, which showed no acute intracranial abnormality.

She reported a history of headache for the past 2 months, which she described as mild, frontal, intermittent, and throbbing in nature, and which improved without medication.

Upon examination she looked well with normal general and neurological exam except for bilateral papilledema and left eye ptosis

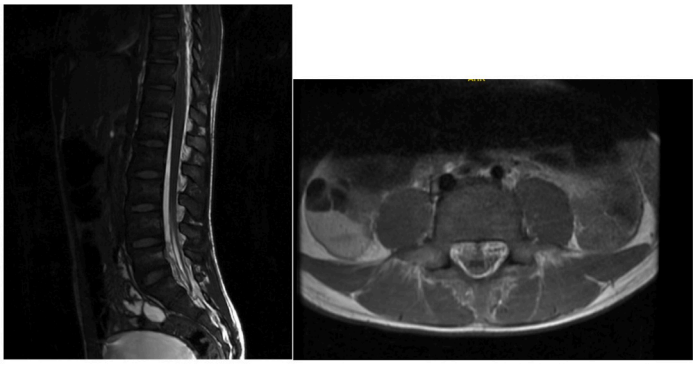

Fig. 1. Sagittal and axial spine magnetic resonance imaging showing thickening and enhancement of the nerve roots of the conus medullaris, cauda equina, exiting nerve roots exiting from L5 to S2.

(reported to be since birth).

The patient was admitted as a case of headache with papilledema for further investigations. Upon active screening of COVID-19, she was found to be positive. A further history of exposure was taken, and her mother mentioned that her father had been admitted to hospital with COVID-19.

A lumbar puncture showed an opening pressure of 22 cmH_2O. CSF analysis revealed WBC 1, RBC 31, protein 0.25, glucose 3.20, and serum glucose 4.8.

Brain magnetic resonance imaging (MRI), orbital MRI, and brain MR venogram, were not done due to social reasons. The patient was discharged on acetazolamide 5 mg/kg/day with an increment planned up to 15 mg/kg/day. An appointment with a neurologist was scheduled for 2 weeks, for follow-up, with brain MRI and MR-venogram to be performed as soon as possible.

3.4. Case 4

A new-born boy was delivered in our hospital on May 23, 2020, during the current COVID-19 pandemic. He was born at 37 weeks by spontaneous vaginal delivery with an APGAR score of 9, 9 at the 1st and 5th min, respectively. A few hours after birth, he was noted to have cyanosis with feeding and was transferred to the NICU as a possible case of transient tachypnoea of new-born. His mother was a 34-year-old lady, gravida 5 para 2, with 2 miscarriages and 2 preterm labors. She was known to have a bicornuate uterus and was followed-up regularly in the Department of Obstetrics and Gynecology during this pregnancy, with an absent vermis and small peri-cardiac effusion on antenatal ultrasound. The Department of Cardiology was involved; an official echocardiogram was performed, which confirmed congenital heart disease, a patent foramen ovale, large peri-membranous ventricular septal defect with a left to right shunt, and a patent ductus arteriosus. Neonatal head ultrasound showed an absent/hypoplastic vermis, with corpus callosum hypoplasia. Upon examination, an active and alert baby with all growth parameters within the 10th centile, including a head circumference of 34.5 cm, subtle dysmorphic features (mainly micrognathia), with normal neurological examination and intact primitive reflexes was found.

His mother clinically deteriorated and developed pneumonia, and required intubation and ventilation. She was found to be positive for COVID-19. At 8 days after birth, the patient developed respiratory distress, which required continuous positive air-pressure ventilation, and he was also found to be positive for COVID-19 in screening.

MRI revealed that the vermis was rotated but present, the corpus callosum was hypoplastic, and there was a left intraventricular hemorrhage, with a small left frontal hemorrhage (Fig. 2). His abdominal ultrasound showed malrotated kidneys, with grade I right and grade III left hydronephrosis. Other investigations, including skeletal survey X-ray and official ophthalmological examinations were unremarkable. Taking into consideration the existence of multiple congenital anomalies, the

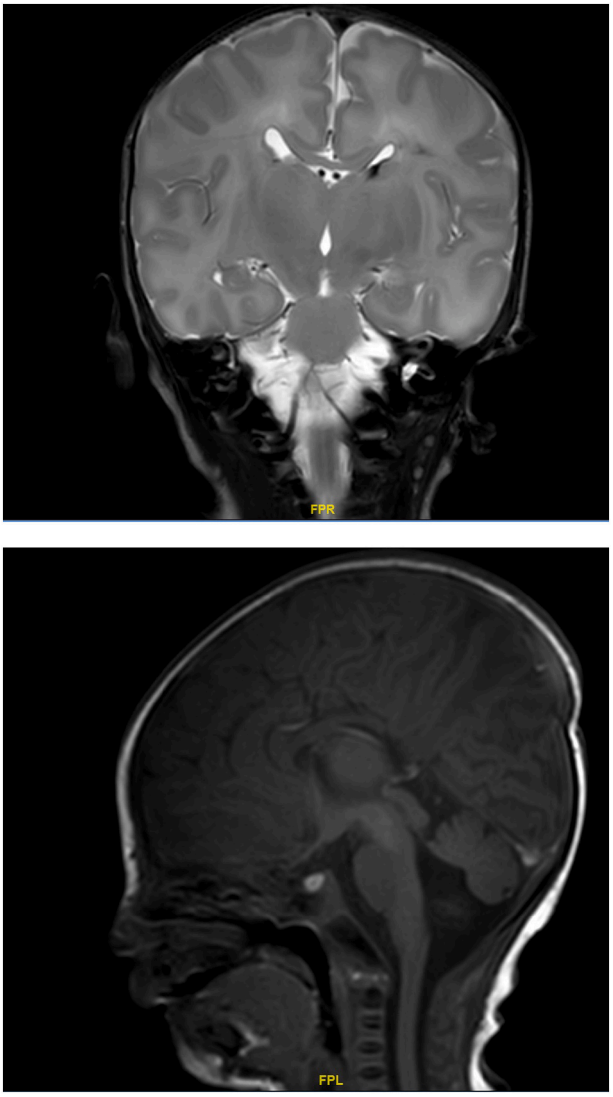

Fig. 2. Magnetic resonance image showing A. Rotated vermis. B. Hypoplastic corpus callosum.

genetic team requested whole exome sequencing to rule out any underlying genetic disease.

The clinical condition of the patient improved with time; however, he was still dependent on oxygen via a nasal cannula. The cardiologist started him on furosemide and captopril. He remains in hospital and the result of his whole exome sequencing is still pending.

3.5. Case 5

A 31-month-old developmentally normal boy was referred to the Pediatric Neurology clinic with a history of abnormal movements noted by his mother since he was 6 months old.

The abnormal movement described by her as a sudden jerk of the bilateral upper limbs, involving the shoulders, which occurred mostly after sleep, with a preserved level of consciousness and no post-ictal symptoms. These abnormal movements happened once to twice per week, 1 week per month.

His general and neurological examination was not remarkable.

EEG performed prior to admission was normal. Thus, the patient was admitted to the hospital for further investigations of brain MRI and sleep-deprived prolonged EEG. As the hospital policy during this pandemic, a COVID swab was taken and tested positive.

EEG and MRI were cancelled, and the patient was discharged home to reschedule his investigations once his infection had cleared (Table 1).

4. Discussion

COVID19 is an emerging disease that is caused by a novel sars-CoV-2. It mainly causes upper respiratory tract infection; however lower respiratory diseases do occur in around 15% of cases which can be sever in 1–5%. Extrapulmonary manifestations have been reported presenting mainly as thrombosis, systemic inflammatory storm or neurological symptoms. Due to the lack of information about COVID-19 neurological manifestations in pediatric cases, this report will provide insight into the association between SARS-CoV-2 and neurological presentation. In our center, we started encountering COVID-19 pediatric cases from the beginning of May 2020; we here described 5 cases presenting with different neurological manifestations.

As this pandemic is unfolding it is becoming clearer that the adult population is the most severely affected by this virus. Recently, a subset group of affected children started to present with neurological manifestation, which we also observed.

The phenomena of those COVID-19 adult patients presenting with neurological manifestation was presented early on, and published cases showed a wide spectrum of presenting symptoms. In a systematic review that included studies published on COVID-19 cases with neurological symptoms, one study was conducted in Wuhan, China, and was a retrospective case series that included 214 cases. They concluded that patients with SARS-CoV-2 infection commonly had neurological symptoms, manifested as acute cerebrovascular diseases, consciousness impairment, and skeletal muscle symptoms. Other studies in this systematic review investigated the manifestations of COVID-19 in general, and within it documented the neurological symptoms that some patients developed [2]. More studies from China and northern Italy were published, specifically discussing the link between Guillain-Barré syndrome and COVID-19, as well as two cases that presented with Miller Fisher syndrome coexisting with COVID-19 infection [3,4].

Comparing adult cases to pediatric cases, the respiratory symptoms of initial infection in COVID-19 were not present in most of the patients, as seen in previously mentioned cases. The 12-year-old girl that developed new onset seizure and was found to have MCA infarction had no prior respiratory symptoms, while the 6 weeks old infant who developed new onset seizure had only mild symptoms of cough and concurrent fever at the same day of presentation [6,7]. On the other hand, 2 cases (from New York) recently reported with cerebral infarction both have severe SARS-CoV-2 infection and were severely affected developing respiratory failure that required intubation and progressing to ECMO which is well known to be associated with high embolic stroke risk [8].

Similarly, there has been an increase in the number of cases of children with COVID-19 who developed a severe systemic inflammatory response to the infection. Consequently, on May 2020, the CDC recognized this response as pediatric multisystem inflammatory syndrome and published guidelines for treating these children. In a study conducted in the UK, among 27 children with COVID-19 pediatric multisystem inflammatory syndrome, 4 developed neurological involvement at some point during their illness. Their symptoms included encephalopathy, headache, brainstem signs, with dysarthria or dysphagia, meningism, cerebellar ataxia, and proximal muscle weakness. In addition, all four children had neuroimaging showing signal changes in the splenium of the corpus callosum. All patients were severely affected and required mechanical ventilation and intensive care admission, but the neurological symptoms were part of the initial presentation in only two of the patients [9].

The association between COVID-19 infection and neurological

Table 1
Summary of cases.

Case	Demographics	Neurological presentation	Investigations	COVID Testing	Treatment	Outcome
Case 1	9-year-old Saudi boy	Dysarthria and gait instability followed by double vision and ophthalmoplegia	MRI spine: thickening and enhancement of the nerve roots of cauda equina and conus medullaris. Positive GQ1b (IgM, IgG) antibodies	Positive Nasopharyngeal swab	Intravenously administered immunoglobulin (IVIG) 2 g/kg over 5 days	Significant improvement
Case 2	6-year-old Syrian boy	Fever and seizure	CSF analysis was reassuring	Positive Nasopharyngeal swab Negative CSF COVID-19 PCR	Antibiotics vancomycin and ceftriaxone were given for partially treated meningitis. Valproic acid 20 mg/kg/day	Normal neurological outcome upon discharge
Case 3	10-year-old Saudi girl	Headache and papilledema	CSF opening pressure: 22 mmH2o	Positive Nasopharyngeal swab	Acetazolamide	Normal neurological outcome upon discharge
Case 4	Newborn Saudi	Congenital heart disease and abnormal MRI findings	Brain MRI: rotated vermis and hypoplastic corpus callosum.	Positive Nasopharyngeal swab	Furosemide, captopril.	Patient is still admitted requiring oxygen
Case 5	31 months old Saudi Boy	History of abnormal movement post-sleep, since the age of 6 months	EEG: normal	Positive Nasopharyngeal swab		Normal neurological outcome upon discharge

manifestations has been discussed in recent literature, and a causal versus coincidental relationship is being debated. Recently published study in November 2020 by Chin et al. was reviewing specifically children who developed multisystem inflammation syndrome (MIS-C) related to COVID-19 infection and found that out of the 187 children, 64 had varying degrees of neurological symptoms, most of which were headaches, positive meningeal signs (meningism), and altered mental status, only few patients underwent cerebrospinal fluid (CSF) study and none of them had a positive SARS-CoV-2 in RT-PCR. The exact mechanism is not very well understood yet, however post-infectious immune response in those case is strongly suggested, which could be similar to the mechanism of COVID-19-related autoimmune meningoencephalitis recently reported in literature about adult COVID-19 patients [11].

In our cases, some of the patients developed pure neurological complaints and were incidentally found to have SARS-CoV-2 by routine screening, with no other causes found to explain their presenting neurological manifestations, similar to our first three cases. The first case developed Miller Fisher syndrome, which is known to be triggered by various organisms that could've been preceding his presentation, however there was no suggestive history of any preceding illness. And during the acute presentation he was having COVID-19, so we presumed that it was the trigger for immune mediated process in Miller fisher variant, and the association with COVID-19 was greatly supported by a number of case reports from multiple countries [3,4]. The second case presented with seizure in sitting of febrile illness without a clear focus, and history of antibiotic usage 2 days before presentation, so the main focus was to rule out CNS infection, keeping in mind the antibiotic patient received prior presentation which could mask the result of CSF analysis. CSF showed leucocytosis however with negative culture and viral screen, as well as CSF COVID-19 PCR, so other organisms especially bacterial could be the cause. The third patient presented with headache history for the past 2 months, and papilledema on ophthalmology examination without any brain mass on imaging, and borderline high CSF pressure suggestive of IIH, patient had none of the known risk factors of IIH, only found to be COVID positive. The last two cases had neurological findings not necessarily related to the virus which discovered by incidence due to active screening. The first patient, A new-born to a COVID positive mother, deteriorated at day 8 of life and found to have COVID positive on screening, however also had congenital heart disease, renal anomalies and brain anomalies which all could be a part of an underlying genetic disease rather than directly associated with COVID.

The second patient, a 31 month old boy with unclassified paroxysmal abnormal movement since age of 6 months, was admitted for investigation and was found in active screening to be positive for COVID. The abnormal movements were present since age of 6 months, clinically those movements were unlikely to be seizure.

Our study highlights the burden of this virus on neurology practices where some investigations were delayed as in our patient, as during this pandemic period, many investigations required for patients are being delayed, which in turn delays diagnosis and treatment. Our patient who had myoclonus since the age of 6 months and was admitted to our center for complete investigations and diagnosis; however, the patient tested positive for SARS-CoV-2 by routine screening, which prevented us from completing investigations.

This study was limited in the number of cases, and lack of SARS-CoV-2 PCR testing in CSF in some patients. A further limitation was the lack of specific investigations needed to confirm diagnosis, such as neurophysiologic studies, EEG, nerve conduction studies, and electromyography, due to the strict infection control protocol at our center.

5. Conclusion

Based on this case series, we conclude that a wide variety of neurological manifestations could be the initial presentation of underlying COVID-19 infection without evidence of respiratory symptoms.

Secondly, the mechanism of central nervous system involvement in COVID-19 infection need to be entertained, an immune mediated process with possible activation of cytokine storm. This might impact in future treatment of such cases in which immune-modulatory therapy can be given.

Lastly, this pandemic place a toll on clinical practice, delaying investigations necessary to achieve a proper diagnosis and treatment for patients. Further cases and epidemiological data are necessary to support a causal relationship between COVID-19 infection and neurological involvement, particularly in children who are asymptomatic or have mild respiratory symptoms of COVID-19 infection, where the neurological symptoms are the initial presentation and are not complications of underlying severe respiratory illness.

Ethical approval

this study was approved by King Abdullah International Medical Research Centre (KAIMRC-IRB) approval #RC20/365/R.

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Data availability

All raw data are available upon request.

Declaration of competing interest

the authors declare that they have no conflict of interest.

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