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Children's Health and Coronavirus Infection: Problems and Ways of Confrontation

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ABSTRACT

The article discusses the features of the problems of infecting children with coronavirus infection and ways to resist this process. The author notes the following: awareness of the coronavirus and testing of its manifestations have increased during the current pandemic, previous reports suggest that pediatric HCoV infections may have been underestimated, especially the cause of febrile seizures and encephalitis has not been fully studied. SARS-CoV-2 and other coronaviruses should be excluded in children with acute onset of neurological disease who have probable risk factors, including age under one year and immunodeficiency.

Studies demonstrate a high probability of worsening of the consequences of the nervous system development, which should be deliberately studied during clinical observation. In general, in order to achieve optimal functional results and quality of life, children with severe neurological diseases caused by coronavirus, including all those who need intensive therapy should undergo longitudinal monitoring of the development of the nervous system to identify obvious and hidden disorders and should be prescribed the therapy.

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INTRODUCTION

The spread of coronavirus infection in the world has decreased somewhat, but doctors continue to fight its spread. Along with adults, children are also susceptible to morbidity, since the virus, mutating, becomes dangerous for them. Of particular concern is that the virus has a progressive effect on the nervous system of children, which in the future may even cause disability in such children. For this reason, it is very important to study the mechanisms of the spread of coronavirus among pediatric patients, assess the complexity of their disease development and determine possible ways to combat complications.

MATERIALS AND METHODS

To write the study, materials were used highlighting the features of the incidence of coronavirus infection in children, the data obtained were compared and analyzed, and appropriate conclusions were drawn upon the fact of the study.

RESULTS

Coronaviruses are single-stranded RNA viruses with a shell that usually penetrate cells through the interaction between their spike-like protein and tissue-specific receptors on the cell surface. In human neurons, spike proteins of both SARS-CoV-1 and SARS-CoV-2 recognize the protein of angiotensin converting enzyme 2, which is also widely expressed in the respiratory tract and gastrointestinal tract .[1]

HCoV spreads through the nervous system in two ways. Hematogenic propagation occurs when circulating monocytes absorb HCoV virions and subsequently express chemokines, increasing the permeability of the blood-brain barrier. Then the virions overcome the blood-brain barrier, which leads to CNS disease. Alternatively, after intranasal infection, HCoV virions cross the lattice plate and infect the olfactory bulbs. After that, propagation from neuron to neuron occurs through exocytosis/

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endocytosis of membrane-surrounded virions through synapses. In addition to direct infection, HCoV sometimes causes secondary painful processes that lead to neurological diseases. For example, in the peripheral nervous system, several reports described Guillain-Barre syndrome (GBS), a post-infectious demyelinating process associated with hyperactivity of macrophages after coronavirus infection in children. In addition, in the Central Nervous System, the recently described "multisystem inflammatory syndrome in children" (MIS-C), similar to Kawasaki disease (KD), after SARS-CoV-2 infection, seems to be associated with an acute neuroinflammatory reaction that predisposes children to cerebral edema, hemorrhage, stroke and aseptic meningitis.

Neurological manifestations of SARS-CoV-2, such as encephalopathy, seizures or peripheral nerve paralysis, have been reported in only a small proportion of children infected with SARS-CoV-2, perhaps in only 1% of cases. It is noteworthy that in a recent series of cases, neurological complications were observed in adults, including headache, changes in mental state and acute disorders of cerebral circulation in 36% of patients.[2] The most severe neurological manifestations of SARS-CoV-2 infection in children were associated with children suffering from MIS-C. For example, a review of the cases of 187 children with MIS-C showed that 34% suffered from neurological damage, with central rather than peripheral manifestations prevailing.

Studies of a number of sources have shown that quite often-neurological symptoms were noted in children who had a coronavirus infection. The World Health Organization (WHO) has recently developed a preliminary case definition of the association of SARS-CoV-2 with neurological diseases. It is important to note that the previous infection is more dangerous for children, taking into account the increased tendency to asymptomatic infection in this population.

The studied sources present clinical cases associated with the development of neurological complications in children who have undergone coronavirus.

Acute flaccid paralysis. Several case reports describe children with clinical features and laboratory studies that correspond to a broad category of AFP, including a more specific diagnosis of post-infectious immune-mediated polyradiculoneuropathy. It is noteworthy that each of these cases corresponded to preliminary WHO definitions in which HCoV were "probably associated" with the neurological condition of the child, including the appearance of symptoms within six weeks after suspected acute infection, the presence of RNA or antibodies indicating infection, and the absence of other probable etiology according to the assessment.

A case was reported of a previously healthy three-year-old girl who developed shortness of breath and inability to walk within one day shortly after the onset of fever, cough and rhinorrhea. Her neurological examination showed bulbar paralysis, characterized by the inability to chew, speak or swallow; reduced motor strength (0/5); lack of deep tendon reflexes. She quickly progressed to respiratory failure requiring intubation.

Her initial assessment was negative, including blood, urine and cerebrospinal fluid tests, as well as electromyography and magnetic resonance imaging (MRI) of the brain and spinal cord. The only positive result was the coinfection of HCoV-229E and HCoV-OC43 in a nasopharyngeal smear detected by reverse transcription polymerase chain reaction (RT-PCR). The authors suspected GBS, one of several etiologies of ORP. After empirical treatment with intravenous immunoglobulin (IVIG), she improved within three days, but after that, she continued to have motor weakness.[3]

Repeated studies of cerebrospinal fluid and electromyography three weeks after admission were normal again. This led to the conclusion that her clinical condition corresponded more to a less specific diagnosis of acute flaccid paralysis, secondary to coronavirus infection, taking into account the known neurotrophic, neuroinvasive and neuroinflammatory potential of leukocytes.

In another case, the patient developed bulbar paralysis, characterized by dysphagia with salivation, weak cough and respiratory disorders, but not requiring intubation. The diagnostic assessment was consistent with GBS, including CSF with albuminocytological dissociation. MRI of the brain and spinal cord showed an increase in the left bulbar nerve complex and anterior and posterior cervical nerve roots. The microbiological assessment was negative, with the exception of HCoV-OC43 according to RT-PCR of the patient's blood. After the injection, his respiratory status and bulbar paralysis improved within a week.

In all three cases, the patients had a general recovery, but a few weeks after admission, their full motor strength had not yet recovered. No long-term outcomes of nervous system development have been reported.

The central cause of AFP, transverse myelitis (TM), has been reported in a child with asymptomatic SARS-CoV-2 infection. Three weeks after the onset of upper respiratory tract symptoms, several family members, all of whom were eventually confirmed to have SARS-CoV-2 infection, a three-year-old girl developed progressive weakness and decreased sensitivity in the extremities. It quickly decreased to sluggish quadriparesis and respiratory failure requiring intubation.[4]

MRI of the spine revealed spinal cord edema with a longitudinally extended lesion involving most of the transverse spinal cord from the inferior medulla oblongata to the mid-thoracic level. CSF studies revealed a slightly elevated protein. An extensive assessment of possible infectious, rheumatologic and autoimmune etiology was negative, except for positive RT-PCR for SARS-CoV-2 from a nasopharyngeal smear preparation. Taking into account the lingering sluggish paresis, her treatment was upgraded to plasmapheresis. Unfortunately, the results of her examination eight days after the appeal remained unchanged, and no long-term results were reported.

Acute multiple encephalomyelitis. Central demyelination due to ADEM has also been reported in children with coronaviruses.

Ye et al. took care of a 15-year-old man, previously healthy, who had irritability, clumsiness of his right hand and difficulty walking for one day. Abnormalities during neurological examination included distal weakness in the upper and lower extremities, dysmetry in the left arm, antalgic gait and decreased vibration and temperature sensitivity below T10. MRI of the brain and spinal cord revealed hyperintensivity in the white matter of the right semioval center and left

cerebellum and non-contrasting spinal lesions at the cervical and thoracic levels, all consistent with the diagnosis of ADEM. HCoV-OC43 was detected in nasopharyngeal secretions, and the assessment for more common pathogens was negative. The symptoms disappeared within a few weeks without therapeutic intervention.

Three months later A follow-up MRI showed a new demyelinating lesion in the left cerebellum and an increase in the size of the right cerebral lesion. Despite these image changes, he did not report any additional symptoms.

This case illustrates the potential of persistent subclinical and severe clinical disorders after acute respiratory infections in children associated with coronavirus infections.[5]

CONVULSIONS

Convulsions, especially simple febrile seizures, were the most frequent neurological manifestation associated with all coronavirus infections among the evaluated cases. Simple febrile convulsions are characterized by short (less than 15 minutes) generalized cramps that occur in the absence of intracranial infection, metabolic disorders or a history of afebrile seizures. Simple febrile seizures are not associated with an increased risk of developing epilepsy or disorders of the nervous system. In particular, the prevalence of HCoV-related simple febrile seizures in children under one year of age has been reported in several series of cases. The researchers found that HCoV-OC43 infections were more common than influenza viruses in this age group. Children with HCoV-related febrile seizures recover well. None of the studies discussed long-term outcomes of nervous system development after febrile seizures caused by HCoV infection. In addition to febrile seizures, the researchers describe the onset of afebrile seizures simultaneously with the mild course of HCoV-HKU1 and one of the respiratory infections SARS-CoV-2 in four-month-old and three-month-old children, respectively.

Researchers also describe cases of epileptic status as a sign of SARS-CoV-2. All the children who were reported to have epileptic status against the background of SARS-CoV-2 recovered, although the medical history did not include a description of the long-term outcomes of the development of the nervous system.

Encephalitis. Encephalitis was the second most common neurological manifestation in children with SARS-CoV-2 and other HCoV. In both reports of cases of encephalitis other than SARS-CoV-2, patients were younger than one year old, immunocompromised and infected with HCoV-OC43.

Blood-stroke. Cerebrovascular events have been reported only in connection with SARS-CoV-2 infections. Similar to the case presented by Freji et al., Essajee and colleagues in Cape Town, South Africa, reported a combination of active M.tuberculosis and SARS-CoV-2 infection in a previously healthy 2.5-year-old girl. Upon admission, the patient had an acute onset of lethargy (Glasgow Coma Scale: 11), dilation of the right pupil with right ptosis, left-sided weakness (arm > leg), general revival of deep tendon reflexes and bilateral extensor plantar reactions. In addition, her cervical lymphadenopathy progressively increased and her appetite decreased. A nasopharyngeal smear for SARS-CoV-2 was positive, and an emergency CT scan of the head showed pan-hydrocephaly, basal meningeal amplification and infarction involving the anterior leg of the right inner capsule, the lenticular nucleus and the thalamus. Cerebral sinus thrombosis was visualized on post - contrast images in the form of multiple filling defects of the venous system, mainly the upper sagittal and transverse sinuses. Gastric aspirate was sent for GeneXpert MTB/RIF analysis, and it turned out to be positive and sensitive to rifampicin.[6]

M.tuberculosis also grew in blood crops. It is noteworthy that she had coagulopathy at admission with an international normalized ratio of 1.63, increased prothrombin time, normal activated partial thromboplastin time and increased fibrinogen and D-dimer. Like Freji and his colleagues, Essaji et al. suggested that SARS-CoV-2 probably caused a cytokine storm that depleted the patient's ability to immunologically respond to both the virus and M.Tuberculosis infections, in addition, it is assumed that the hyperinflammatory reaction led to endothelial damage, which aggravated her coagulopathy and stroke risk.

This patient survived and after a month of intensive neurorehabilitation regained the ability to take oral nutrition, but she still had residual left-sided hemiparesis. The report does not mention her potential long-term deficit in the development of the nervous system.

Two additional case reports describe focal cerebral arteriopathy characterized by narrowing and bands of the left medial cerebral artery with acute infarctions of the left insula and basal ganglia in children with a positive test for SARS-CoV-2.

In both cases, the additional etiological assessment was unremarkable. Based on current data obtained from the adult population, the authors hypothesize that these strokes were secondary to the cytokine storm SARS-CoV-2, leading to focal vasculitis caused by inflammation.

MIS-C. WHO has characterized MIS-C according to a six-part definition that includes childhood age, persistent fever, laboratory signs of inflammation, signs or symptoms of organ dysfunction, lack of an alternative diagnosis, and the close onset of SARS-CoV-2 infection or impact.

Among patients suffering from cerebrovascular diseases, children with MIS-Z showed more signs of microvascular infarctions in deep structures of the brain compared with cerebrovascular manifestations in patients without MIS-Z.

Regev et al . A 16-year-old man, previously healthy, was reported to have fever, sore throat, fatigue and abdominal pain three weeks after exposure to SARS-CoV-2. Upon admission, he had a headache and stiffness of the occipital muscles, and on the third day of hospitalization, he developed heat shock, which required intubation.

Initially, nasopharyngeal smears for SARS-CoV-2 were negative, but after clinical decompensation, he had a positive nasopharyngeal smear and associated serological confirmation of past SARS-CoV-2 infection with positive IgG and IgA antibodies. The initial CT scan of the head was negative, but MRI/magnetic resonance angiography of the brain revealed diffuse small weakly signaled foci of hemosiderosis in the subcortical

white matter of both hemispheres and the corpus callosum, indicating an inflammatory process of the microcirculatory bed of the brain. The patient as a whole recovered from MIS-C without obvious cognitive impairment, although he had constant weakness.[7]

The researchers reported two cases in boys aged 9 and 12 who developed a fever and changed their mental state. In both cases, MRI of the brain revealed limited diffuse lesions throughout the corpus callosum. Both patients were diagnosed with MIS-C and had a rapid response to immunotherapy. In a nine-year-old patient, repeated MRI showed almost complete resolution of lesions of the corpus callosum, indicating that the alleged micro infarctions were probably secondary to an inflammatory, possibly cytokine-mediated mechanism.

In addition to cerebrovascular lesions, atypical neurological manifestations of other neurological disorders were observed in children with MIS-C.

DISCUSSION

In this preliminary review, we evaluated the literature on cases of HCoV infection in the nervous system in children to get an idea of the expected consequences for the development of the nervous system of pediatric SARS-CoV-2 infections. Six of the seven HCoVs, with the exception of MERS-CoV, were associated with either primary or secondary neurological disorders in children. In the most severe form, cases of HCoV infection were associated with ORP, ADEM, encephalitis, epileptic status and stroke. Especially noticeable were CNS lesions associated with MIS-C, secondary to SARS-CoV-2 infections, which included infarctions of large vessels and microvessels of the brain, secondary pseudo tumors of the brain.

Deaths have been reported in several children with neurological disorders after MIS-C. In less severe cases, HCoV infections were associated with febrile seizures, especially in infants, and focal nerve paralysis. Taken together, these reports illustrate the rare but established ability of HCoV to cause severe neurological diseases leading to ongoing functional disorders. In addition, there is extensive literature demonstrating the ability of HCoV to cause severe systemic diseases requiring intensive therapy, which in itself is a risk factor for disorders of the development of the nervous system.

Accordingly, there is a need to use monitoring of the development of the nervous system to identify long-term consequences of development and behavior.

Monitoring the development of the nervous system can be intuitive for many of these diagnoses in many clinical practices of pediatric neurology. However, there are differences in the duration of monitoring, the degree of evaluation and the availability of testing options. Rapid global skill recovery may mask more subtle long-term but harmful deficits, some of which may manifest years later when a child is expected to develop a particular skill. Many of these deficits are either not obvious before discharge from a neurological hospital, or are not detected specifically in the clinic and can subsequently persist without additional evaluation.[8]

In addition, the role of a neurologist in managing the consequences of development and behavior is not standardized, while some service providers prefer to direct deficits related to learning, behavior and motor functions to colleagues from pediatrics specializing in developmental and behavioral pediatrics, psychiatry, physiotherapy and rehabilitation, respectively.

It is possible to draw certain conclusions within the framework of predicting the impact of childhood SARS-CoV-2 infections on the development of the nervous system.

Acute flaccid paralysis primarily affects peripheral nerves, whereas acute flaccid myelitis (AFM) and TM are immune-mediated conditions affecting the central nervous system, especially the spinal cord. In the category of ORP, GBS, AFM and TM manifest significant weakness and potentially respiratory depression. Despite the persistence of weakness at the onset of the disease, the reported outcomes reveal greater variability in long-term motor strength and function for all three pathologies.

In general, almost half of the children recover completely, although people with persistent weakness may have significant functional disorders. In addition, constant sensitivity disorders and bladder dysfunction are often observed. Children with AFP of any etiology, including GDS, TM and AFM associated with SARS-CoV-2, should be under long-term monitoring of the development of the nervous system.

Children with febrile seizures should be regularly examined by their attending physicians for the presence of common signs and symptoms of consequences for the development of the nervous system after SARS-CoV infections-2. Those with severe symptoms, including epileptic status, should receive appropriate follow-up monitoring of the development of the nervous system and neuropsychology.[9]

Acute multiple encephalomyelitis is a predominantly monophasic immune-mediated inflammatory demyelinating disease of the central nervous system, which usually occurs after a viral infection. A recent meta-analysis has shown that global neurocognitive consequences (for example, mental retardation) are not observed after the ADEM. However, a significant proportion of children, from 20% to 43%, demonstrate specific but persistent violations of sustained attention and information processing speed.

Survivors of childhood encephalitis have long-term neurological consequences, ranging from neurocognitive disorders and related learning problems to behavioral and personality changes. Any cases of SARS-CoV-2 encephalitis require monitoring of the development of the nervous system.

Outcomes after stroke in children are more nuanced than the understanding of neuroanatomy based on localization, since recovery after stroke in children occurs in the context of innate brain development processes, which differ depending on age, neuroplasticity and the sequence of recovery after brain injury. In addition, long-term functional deficiency after stroke in children depends on the mechanism and degree of damage. Strokes of large vessels usually lead to corresponding disorders of the function controlled by this area, whereas micro bleeds can lead to more subtle cognitive or behavioral disorders that are difficult to predict. However, with all the etiologies of childhood stroke in the existing literature, there is a large variability in the degree of this deficiency.

Thus, in the absence of current clinical knowledge about the recovery of children after a stroke caused by SARS-CoV-2, taking into account the degree of trauma and the early clinical course of the disease in a child can determine the aggressiveness of rehabilitation. However, even if there are no serious disorders, children with cerebrovascular diseases associated with HCoV infection should undergo follow-up monitoring of the development of the nervous system to assess the disorders resulting from minor disorders of neural connections.

Multisystem inflammatory syndrome in children, or MIS-C, is currently an established manifestation of SARS-CoV-2 infection observed in the pediatric population. As a hyperinflammatory syndrome, MIS-C has been compared with childhood vasculitis, which, first, can lead to coronary artery aneurysms, and can lead to other neurological consequences and consequences of the development of the nervous system.

HCoV can also cause critical illnesses, regardless of whether they are associated with neurological manifestations of the disease or not, especially in young children and children with immunodeficiency. This potential is well illustrated by a recent report on 48 children with SARS-CoV-2 admitted to the intensive care unit. In this study, 68% of children were classified as "critically ill", 38% - needed a ventilator, 25% -needed vasoactive support, and the average length of stay in the intensive care unit exceeded 2.5 days.[10]

Children in critical condition, even without neurological damage, are at high risk of acquired functional deficiency after discharge from the intensive care unit. Up to 81.5% experience a decrease in one or more functional areas six months after admission to the intensive care unit, and functional disability increases over time after discharge. Thus, children admitted to the intensive care unit in connection with SARS-CoV-2 should undergo follow-up monitoring of the development of the nervous system, regardless of the infectious picture.

CONCLUSION

Thus, it can be concluded that awareness of the coronavirus and testing of its manifestations have increased during the current pandemic, previous reports suggest that pediatric HCoV infections may have been underestimated, especially the cause of febrile seizures and encephalitis has not been fully studied. SARS-CoV-2 and other coronaviruses should be excluded in children with acute onset of neurological disease who have probable risk factors, including age under one year and immunodeficiency.

Studies demonstrate a high probability of worsening of the consequences of the nervous system development , which should be deliberately studied during clinical observation. In general, in order to achieve optimal functional results and quality of life, children with severe neurological diseases caused by coronavirus, including all those who need intensive therapy should undergo longitudinal monitoring of the development of the nervous system to identify obvious and hidden disorders and prescribe therapy.

Author Contributions

All authors contributed in reviewing the final version of this paper.

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