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Neurological complications after covid-19 in children

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Abstract

Studies have shown that during the pandemic period, children under 5 years of age accounted for 1.8% of COVID-19 cases. After covid complications are now a major concern and represent a new disease entity known as PIMS and MIS-C. Many studies have been conducted on the pathomechanism of the virus and the clinical manifestations it causes in adults, including neurological complications.

Symptoms are mainly associated with central and peripheral neurological disorders, ranging from mild (headache, fever, cough, pharyngitis, rhinitis and anosmia) to severe (stroke or Guillain-Barré syndrome). Dyspnoea or respiratory failure is seen in approximately 11.7% of young patients. Although SARS-CoV-2 mainly occupies the respiratory system, about 10% report gastrointestinal symptoms. CT abnormalities of the chest of children are less frequent and milder than in adults, and include opacities of frosted glass and patchy shadows. In many cases, elevated CK-MB levels have also been noted, indicating possible myocardial damage.

Children and adolescents contribute to an increasing proportion of all Covid-19 cases. It can be due to the emergence of highly infectious variants of the virus. Many drugs have been tried in children both antiviral, antimalarial, corticosteroids and intravenous immunoglobulin or selective cytokine brokers. The only effective method of prophylaxis is two doses of BNT162b2 vaccine given 21 days apart.

Key words: covid-19 in children, treatment of covid-19, neurological complications of covid-19

1. Introduction

Since November 2019, when severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was first reported in the media worldwide, many studies have been conducted on the pathomechanism of the virus and the clinical manifestations it causes in adults, including neurological complications such as cerebrovascular damage, encephalitis or encephalopathy, and neuromuscular disorders. However, the number of medical cases describing neurological symptoms in Covid-positive paediatric patients is small and many questions remain unanswered [1].

2. Emergence of covid-19 disease

2.1 Pathophysiology of SARS-CoV-2 infection

SARS-CoV-2 is a representative RNA virus of the family Coronaviridae. This virus uses the naso-oral route to infect the human body. It induces interferon (IFN) production in the body, which is part of the body's natural, innate way of fighting the pathogen. However, IFN is responsible for the increased expression of angiotensin-converting enzyme 2 (ACE2), which interacts with the receptor-binding domain (RBD) of protein S on the virus surface. After proteolytic cleavage of this molecule by transmembrane serine protease type II (TMPRSS2), host-virus membrane fusion is possible, resulting in pathogen entry into the host cell. [2].

There are reports of vertical transmission of SARS-CoV- 2, but the possibility and mechanism are still poorly understood. Placental and fetal tissue can express ACE2, demonstrating that infection of the fetus during pregnancy is possible. The number of these receptors appears to increase as pregnancy progresses, increasing the risk of transmission (especially in the third trimester) and potential neurological complications in the newborn [1].

2.2 Radiological and laboratory findings

Recent data suggest that radiological abnormalities on chest imaging in children are quite similar to those in adults, but occur less frequently and present milder changes [3] [4]. Ground-glass opacities (GGO) and macular shadowing are most commonly found on chest CT, as in adults [5]. The location of these pathological changes is observed in the middle and outer zones of the lung or under the pleura. GGO may present with unilateral or bilateral dissemination [6]. Laboratory findings in adults with COVID-19 have been described in many studies and are fairly well known and predictable. At present, the same results in children require further study. Current reports indicate that the leukocyte index is not a reliable marker of COVID-19 severity in children, as it is used in adults, due to its inconsistent pattern. Although, significant elevations in c-reactive protein (CRP), procalcitonin (PCT) and lactate dehydrogenase (LDH) were observed in severe disease. This result was consistent, suggesting its usefulness in monitoring the course of the disease in paediatric patients. Elevated creatine kinase-MB (CK-MB) levels were noted in mild cases, suggesting possible cardiac damage and highlighting the importance of monitoring cardiac biomarkers during further hospitalisation of children [6].

2.3 Characterisation of the disease course

Fever and cough are the most common paediatric manifestations of COVID-19, occurring in approximately 50% of infected children [7]. The cough is mostly dry, but can sometimes be productive in more severe cases. A runny nose, nasal obstruction and sore throat are reported by almost 20% of children [8].

Many paediatric patients have also had COVID-19 pneumonia, with dyspnoea or respiratory distress observed in approximately 11.7% of young patients. Although SARS-CoV-2 is mainly a respiratory virus, gastrointestinal symptoms including: diarrhoea, abdominal pain and vomiting are reported in 10% of children. Myalgia has been observed in approximately 19% of patients [8].

Since the beginning of the pandemic, children have been observed to have milder symptoms compared to adults. The youngest children are often asymptomatic, in a Chinese review of 29 studies that included 4300 children, 19% had no symptoms and 37% had no radiographic abnormalities [7].

Paediatric inflammatory multisystemic syndrome temporally associated with severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2) (PIMS-TS), also known as childhood inflammatory multisystemic syndrome (MIS-C), is a new acute systemic inflammatory disease that occurs in children approximately 3-6 weeks after acute SARS-CoV-

2 infection or contact with an infected person. The most common symptoms come from the gastrointestinal, respiratory and cardiovascular systems. However, neurological symptoms occur in 11% to 30% of previously infected children [9].

The risk of reinfection with COVID-19 virus in children is very low. In children with a wellfunctioning immune system, reinfection with the virus is not life- and health-threatening. Reinfection in immunocompromised children is much worse. Even after vaccination, doctors recommend a booster vaccination to alleviate later symptoms of the disease. One case of a 16year-old patient with MIS-C who became reinfected with COVID-19 virus was reported. The symptoms of infection were mild because immunity persisted for at least 8 to 12 months after infection. The patient had no fever or other symptoms of MIS-C, and inflammatory markers remained low. Re-infection did not result in recurrence of MIS-C. Due to the different course of re-infection in children, countries have started vaccinating children from the age of 12 years [10] [11].

2.4 Treatment methods

An important part of the fight against SARS-COV 2 is adequate prophylaxis and prevention. If infection with the virus is suspected, those around the child should take every precaution, including the use of disinfectant liquid for hands, hospital equipment and flat surfaces[12]. When a child develops a fever (> 38° C), cool compresses and antipyretics should be used [1]. When a child is hospitalized, the most important aspect is to control the patient's intake of adequate amount, ensuring at least a minimum amount of calories. The next step is oxygen therapy and drug supplementation [12]. The aim of treating children is to prevent organ failure, ARDS secondary to nosocomial infections [4].

Throughout the COVID-19 pandemic, many drugs have been tested and tried in children, whether antiviral, antimalarial, corticosteroids, intravenous immunoglobulin or selective cytokine brokers [12].

To date, interferon alfa-2b administered by nebulisation is the only well-studied and described drug that has been used to control the disease [3]. Zhejiang University School of Medicine has published recommendations that interferon and oral lopinavir/ritonavir with corticosteroids can be used when complications such as haemophagocytic syndrome, encephalitis or septic shock occur. However, WHO does not recommend any specific treatment in children [12].

Chloroquine, which in vitro inhibited the entry of SARS-COV 2 into cells, was also used in young patients during therapy. In addition, its immunomodulatory effect was considered [4]. The MOHFW allowed the use of hydroxychloroquine in combination with azithromycin only in children older than 12 years [12].

3. Complications of severe infection and difficulties in treatment

Recent reports indicate that the incidence of the disease increases with age. Postcovid complications are now an important problem. These complications represent a new disease entity referred to as PIMS or MIS-C. It was first described in May 2020. Sagar S. Lad et al. described clinical cases of 4 children diagnosed with PIMS in July 2020 [13]. The patients presented with neurological symptoms. One patient (a 2-year-old boy) developed seizures with persistent fever. Cerebrospinal fluid (CSF), EEG and MRI examinations showed no abnormalities. Another patient had Kawasaki disease and excessive sleepiness and sluggishness. As in the previous child, CSF, EEG and MRI studies were normal. A 7-year-old boy presented with seizures with encephalopathy. Cerebrospinal fluid examination showed no abnormalities, but MRI showed signal changes in the splenium of corpus callosum (SCC). EEG showed diffuse slow activity. The last case was a 13-year-old patient who suffered a concussion. MRI and cerebrospinal fluid examination were not performed [14].

Omar Abdel-Mannan et al. described neurological and radiographic findings associated with COVID-19 virus infection in children [14]. The study included 50 children infected with SARS-CoV-2. PIMS was diagnosed in 27 patients. Neurological symptoms were present in 4 children, representing 14.81% of all children diagnosed with PIMS. Symptoms related to neurological involvement occurred for the first time in 2 children - 7.41%. All four patients had encephalopathy, peripheral nervous system involvement, with global proximal muscle weakness. Three of the four children with neurological activity reported headaches. One child had meningeal symptoms. One patient also had cerebral ataxia. All four patients had signal changes in the corpus callosum (SCC) [15].

Prateek Kumar Panda et al. presented a systematic review and meta-analysis that included 3707 patients with neurological complications after COVID19 aged less than 18 years [15]. 623 patients presented non-specific/specific neurological manifestations, 581 had non-specific neurological manifestations and 42 patients represented specific neurological manifestations. The most common complications were headache, myalgia and fatigue, which occurred with a frequency of 16.7%. The rarest complications were Guillain-Barre syndrome, intracerebral haemorrhage. Of the children with specific symptoms, 25 had encephalopathy, 17 had meningeal symptoms and 12 had seizures. A case report of a 17-month-old girl diagnosed with Acute Disseminated Encephalomyelitis (ADEM) is described [16]. The parents noticed unsteady gait, fatigue and weakness. 13 days before the presentation, the girl had been feverish for 5 days (maximum temperature was 38.9°C). In hospital, the patient was found to have positive Brudzinski sign, significant neck stiffness, right upper limb paresis and left limb stiffness. Laboratory investigations revealed increased inflammation. Magnetic resonance imaging showed multisite hyperintense signalling at T2. Cerebrospinal fluid analysis was also performed and showed mild pleocytosis with lymphocyte predominance. No bacteria were detected in the CSF. Enterovirus and rotavirus pathogens were also not detected. IgG antibodies against SARS-CoV were present in the serum. The patient's dad had tested positive for 3 months before the onset of the child's symptoms. On the second day of hospitalisation, the girl developed increased lethargy and autonomic instability. She was transferred to the intensive care unit. IVIG therapy was started at a dose of 2 g/kg for 4 days. Methylprednisolone at a dose of 30 mg/kg daily was also administered for 5 days. After another 3 days the girl was transferred to the general paediatric ward. Two months after discharge from hospital, neurological examinations showed no abnormalities. Medical reports have highlighted that a significant number of adult patients developed symptoms such as loss of smell after COVID-19 infection [17]. This symptom has also been described in the paediatric population. In a study involving 236 paediatric patients infected with COVID-19 virus, anosmia/dysgesia was reported in 12.3% [18].

4. Vaccination of children reduces COVID-19 infection

Vaccination has been shown to be effective for COVID-19 virus infection in children. They are safe to use and effectively reduce transmission of the virus, further reducing complications of infection. The current omicron virus variant is more resistant to vaccination than previous variants. It has mutations in the FMD protein that affect the neutralising antibody response. Children and adolescents should also be vaccinated with a third dose to provide better protection against infection [19].

5. Discussion

According to WHO, between 30 December 2019 and 13 September 2021, children under 5 years of age accounted for 1.8% of global COVID-19 cases and 0.1% (1,721) of global deaths, while adolescents (5-14 years) accounted for 6.3% (6,020,084) of global cases and 0.1% (1,245) of global deaths [20]. Various studies involving 3,700 paediatric patients with COVID-19 showed that 17% had non-specific neurological conditions. Moreover, in children with Multisystem Inflammatory Syndrome in Children (MIS-C), these symptoms were present in more than half of the cases [21].

Children with SARS-CoV-2 infection are more mildly ill than adults. The most commonly reported symptoms include fever, cough, pharyngitis and rhinitis. Neurological symptoms are mainly headache and anosmia. Few case reports have described more severe complications such as Guillain-Barré syndrome, ischaemic stroke or MIS-C [21]. It is still unclear what accounts for this difference. Some evidence points to lower levels of ACE2 protein expression in children in the nasal epithelium, the site of viral entry. Other reports suggest that children have pre-existing immunity protecting them from severe lower respiratory tract diseases such as COVID-19 due to frequent seasonal exposure to multiple viruses [22].

Many reports in both adults and children have associated COVID-19 with a variety of central and peripheral neurological damage, ranging from mild symptoms such as headache and anosmia to severe manifestations such as stroke, seizures and encephalopathy. SARS-CoV-2 appears to infect a smaller proportion of the pediatric population than adults and causes much more mild morbidity. Many children appear to be asymptomatic [23]. Perhaps the main reason is the low expression of ACE2 receptors in the nasal epithelium of children, and the pediatric population appears to be less susceptible to neurological symptoms [22]. In many parts of the world, children and adolescents account for an increasing proportion of all cases. Research

indicates that this is due to the emergence of highly infectious variants of the virus [25]. A safe and effective vaccine is the best way to contain the COVID-19 pandemic, which has caused over 4 million deaths to date[24].

The US Centers for Disease Control and Prevention (CDC) recommended Pfizer's COVID-19 vaccine containing mRNA (messenger RNA) for children aged 5 to 11 years - or 28 million children. However, surveys show that between 42% and 66% of parents of these children are unwilling or unable to use this protection [25].

Two 10-µg doses of BNT162b2 vaccine given 21 days apart were safe, immunogenic and 90.7% effective against Covid-19 in children aged 5 to 11 years [26].

6. Conclusions

SARS-CoV-2 appears to infect a smaller proportion of the paediatric population than adults and causes a much milder form of the disease. In most cases, the course of Covid 19 virus infection is mild or asymptomatic. The risk of serious complications or death is relatively low compared to adult patients. The number of studies on the course of covid virus infection in children is small. Further epidemiological studies should be conducted to help develop methods of prevention and treatment of covid 19 virus infection in children.

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