

Neurologic Manifestations of COVID-19 Disease in Children and adults

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Editor Note

SARS-CoV-2 has kept the world on tenterhooks for half a year. In this short time, millions of data and clinical findings have been collected, the amount of which astonishes even the scientific community. But the majority of them concern adult patients. Knowledge about the clinical course, complications and therapy of COVID-19 in children and adolescents, on the other hand, has been limited to date [2]. And the data that have been collected internationally illustrate once again that "children are not small adults." This is because the incidence of infection in this age group appears to differ, in some cases markedly, from that of elderly and senior patients.

The first pediatric case was reported from China on January 20: A 10-year-old boy from Shenzhen who had visited the city of Wuhan with his family was affected. Why are there differences in the number and type of diseases between adults and children is yet not completely understood. What virological and immunological findings already exist that could explain these phenomena? There are 2 theories for the difference between children and adults: One is that there is a different density of ACE2 receptors on lung epithelial cells, the nasopharyngeal epithelium, and the intestinal epithelium depending on age. The ACE2 receptors are the crucial "contact points" for SARS-CoV-2 to enter the cells of the human organism. The other theory,

which Protzer says may be more likely, focuses on a specific B-cell fraction. Children have more memory B cells compared to adults, which form more broadly effective IgM-type antibodies and thus can protect children from severe disease progression. In adults, the B-cell response shifts. They respond more specifically to pathogens that the body has dealt with a before-for example, through vaccination. Evolutionarily, the immune system at a young age is designed for children to survive. The first antibody protection comes from the mother, so the child's organism can respond to pathogens that its immune system had never faced before. The longer you live, the more this immune response shifts into a very

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pathogen-specific response. Researchers emphasize that coronaviruses are not the first viruses to cause different reactions in the host organism, depending on the age of the person. Strikingly, the microbiome is composed differently in the first 3 years of life than later. Then the normal body flora fights against any invaders from outside. And both parties try to control each other. That is, many levels exist that terminate immunological differences between children and adults. What role SARS-CoV-2 plays in this is unclear. Therefore, there will be no simple explanation. Several infections in early life are associated with very high viral loads, even though the children are clinically healthy. This is true for HIV, for example. The question arises: if viral loads in children are even higher than in adults, can they infect others more quickly or more severely? The transmission of SARS-CoV-2 infection is mainly through adults, especially through household contacts, according to different studies. One study showed that symptom onset in 7 infected children was preceded by confirmed COVID-19 infection in adult family members. In another study, 28 of 31 infected children were found to have other ill family members. In contrast, the so-called Heinsberg study reported a significant increase in the risk of infection for other family members when an infected child lived in the household. Data from Germany show that in symptomatic children, the SARS-CoV-2 viral load at the time of diagnosis is comparable to that of adults. A survey from Switzerland demonstrates that symptomatic children of all ages shed infectious virus during the early phase of the illness. Infants shed larger amounts of virus. Different authors substantiate this with a laboratory

peculiarity: the infants' samples had a low "Ct value" in the polymerase chain reaction. The Ct value indicates the number of multiplication cycles required to detect viral genes. A low Ct value corresponds to a high viral load. The Ct values were unusually low in the infants, the publication states. In one infant, the test compound even had to be diluted to determine a Ct value at all. In 18 of the infants under 90 days of age, the infection had been discovered rather accidentally. According to the pediatrician Leena Mithal, the cause was often the fact that there had been other illnesses in the family. All infants were only mildly ill: 14 had a fever, 8 coughed, and 6 had gastrointestinal symptoms (vomiting and diarrhea). However, the study results published so far internationally on SARS-CoV-2 infection in children are partly contradictory. As a reminder, the Berlin virologist Prof. Christian Drosten had also shown in a much-discussed preliminary publication of a study that there was no significant difference between viral loads in individuals aged 1-20 years compared with adults. However, the mere presence of viruses in the respiratory tract does not prove that they are also highly disseminated. For example, a 9-year-old boy infected with SARS-CoV-2 did not pass on the infection despite numerous social contacts. The infectivity of SARS-CoV-2-infected children may be subject to wide interindividual variation. In addition, it cannot be ruled out that children in "lockdown" situations had fewer exposures outside the home than adults. In addition, there is the possibility that children had been infected beforehand without being detected and were thus immune at the time of the study. According to the

"COVID-19 Children Study" from Baden-Württemberg, Germany, children are less likely to become infected with coronavirus than their parents. Therefore, they should not be considered as drivers of the infection wave, said Prof. Klaus-Michael Debatin, MD, Ulm, Germany. Children aged 1-10 years and one parent each were screened for current or survived SARS-CoV-2 infection. The total study population included 5 042 subjects (2 521 children and 2 521 corresponding parents). The present interim analysis was performed on 4 932 subjects. Here, only one parent-child pair tested positive for SARS-CoV-2 RNA (0.04%); they had only mild symptoms. Children are rarely seropositive. Sixty-four tested had formed IgG antibodies and passed through infection largely unnoticed, corresponding to a seroprevalence of 1.3% (95% CI 1.0-1.7%). Overall, 19 children (0.8%; 95% CI 0.5-1.2%) and 45 parents (1.8%; 95% CI 1.3-2.4%) were seropositive. The difference in antibody formation between children and adults was highly statistically significant. Seroprevalence differed by age group (1-5 years: 0.6%; 6-10 years: 0.9%; parent group: 1.8%). Thus, the children tested were less likely to be infected than adults. The study does not answer the question of how infectious children are. It should also be noted that the results are not directly transferable to the population as a whole, since the participants were not randomly selected, Debatin said. "Overall, therefore, children appear to be not only less likely to contract COVID-19 but also less likely to be infected by the SARS-CoV-2 virus." The results of the study also did not allow any conclusions to be drawn about who was first infected in a family. According to a recent study by the Rostock University

Medical Center in Germany, the risk for children to become infected with SARS-CoV-2 is lower than for adults.

Neurological symptoms and COVID-19

Many studies have described neurological and psychosocial manifestations of COVID-19 [3,4,5]. The spectrum ranges from olfactory disorders to severe strokes [6,7]. An Italian paper now showed that 88% of affected individuals are not symptom-free after acute disease. In some cases, neurological symptoms and deficits remain. Spanish flu also resulted in permanent neurological problems. Are both cases virus-mediated autoimmune reactions? A neuro-immunological research group at the Charité University Hospital found antibody findings indicating that the immune system may target the body's nerve cells in severely ill COVID-19 patients. The immune system may target the body's nerve cells in severely ill COVID-19 patients. Numerous case reports and studies now describe accompanying neurological symptoms in COVID-19 patients. Olfactory and gustatory disturbances are very common [6]. However, diffuse brain damage (encephalopathy) with neurological and psychiatric abnormalities, inflammation of the brain and spinal cord (encephalomyelitis) or strokes can also occur during the virus infection [8]. The curious thing is that the latter occurs not only in COVID-19 patients who have many cardiovascular risk factors but also in young, "vascular healthy" people who have become infected with SARS-CoV-2. Peripheral nervous system disorders such as Guillain-Barre syndrome may also occur as a result of the viral infection. Based on these observations, international experts

are already talking about "neuro-COVID" (10). It is still not clear for some of the neurological manifestations how common they are in COVID-19 [3-9]. But even if the percentage were only about the same as SARS or MERS, the absolute number of COVID-19-associated neurological diseases must be considered high, given the enormously high infection rates worldwide, and this must be taken into account in inpatient care. Also troubling is the finding that neurologic symptoms often persisted. The Spanish flu of 1918 also led to unexplained neurological symptoms as a result, with more than a million people suffering for another decade. This shows that neurological follow-up of COVID-19 patients with appropriate further diagnostics is enormously important. The neuroinvasive potential of coronaviruses was already described in 2002/2003 during the SARS-CoV outbreak: In this case, the viruses were found only in brain cells, not in the neighboring blood or lymph vessels, which suggests a route of infection via the nerve cells and not via blood or lymph vessels. In the case of SARS-CoV-2, however, direct virus detection in the cerebrospinal fluid (CSF) has so far only been successful in isolated cases. This leads to the hypothesis that mainly indirect viral-mediated mechanisms could play a role in the development of neurological symptoms. In conclusion, COVID-19 infection in children and adults are completely different in many aspects, introducing new entities like MIS-C in children, and especially reveal neurological diseases and treatment. To date, the pathogenesis in neurological aspects in COVID-19 is still not completely understood and need further intensive research.

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