


Neurological Symptoms as (Post) Pandemic Burden in Children and Adolescents-Single Tertiary Center Experience from Croatia

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ABSTRACT

Objectives: Although COVID-19 primarily affects the respiratory system, the central and peripheral nervous system may be involved. Neurological manifestations of COVID-19 infection occur in acute or post-acute stages and may persist as long-lasting symptoms known as “long-COVID” or “post-COVID-19”. This study aimed to investigate the clinical profile, outcomes, and management of neurological manifestations after COVID-19 infection in children.

Materials & Methods: A retrospective chart review was conducted of all pediatric patients admitted to our tertiary pediatric center with neurological symptoms following COVID-19, meeting criteria for long COVID-19/post-COVID-19, from December 2020 through the end of 2021, with a one-year follow-up period.

Results: Eighty-four patients were included (median age 12.7 years; range, 0.5-18 years). Girls were more affected than the boys (female n = 51; 60.7%, $\chi^2 = 3, 86; p = 0,049$). The most common neurological manifestation were headache (n = 47; 55.95%), dizziness (n = 19; 22.6%), visual disturbances (n = 9; 10.7%), afebrile seizures (n = 6; 7.1%), and anosmia/hyposmia (n = 4; 4.7%). Overall, 19 (22.6%) patients required psychological support, of whom 4 (4.8%) patients required psychiatric consultation due to suspected mental disorder. The most significant number of patients with neurological symptoms after COVID-19 was observed between October 2020 and March 2021 (n=44, 52.4%).

Conclusion: The obtained findings align with the results from similar studies and show that neurological manifestations after COVID-19 infection appear more frequently in school-aged children, predominantly in female patients. Neurological post-COVID-19 symptoms require medical attention to exclude more severe conditions.

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Introduction

Although COVID-19 primarily affects the respiratory system, other organs may be involved, including the central and peripheral nervous systems. Various neurological manifestations occur in the acute or post-acute stage of infection and include mild, as well as serious and life-threatening conditions. In

addition to coronaviruses, common respiratory viruses with central and peripheral neurological manifestations include influenza, metapneumovirus, respiratory syncytial viruses/orthopneumoviruses, enteroviruses (D68, A71), and others (1-4). A spectrum of neurological manifestations may persist, occur, fluctuate, and relapse over time after COVID-19 infection as long-lasting symptoms known as “long-

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COVID-19” or “post-COVID-19” (5-7). Acute neurological manifestations are expected in severe infection; however, post-acute neurological manifestations of COVID-19 may occur after either mild or severe infection (2). Although children, compared with adults, represent a highly susceptible group for respiratory tract infections, a lower tendency for COVID-19 infection (and persistent manifestations) has been observed (4). Children with COVID-19 infection are often asymptomatic (43-68%) or with mild illness and complete recovery within three to four weeks (6, 8). Post-acute neurological manifestations after COVID-19 infection seem to be more frequently reported in children with variable prevalence, which is relatively rare (9,10). Nevertheless, it is crucial to recognize these manifestations and distinguish them from a more severe condition known as multisystem inflammatory syndrome in children (MIS-C). Although the pandemic has ended, the virus persists in the population, and more attention is being given to post-COVID-19, which has been recognized as a clinical entity and included in the ICD-10 classification (7). Nonetheless, before the official determination of the pandemic, the World Health Organization recognized post-COVID-19 condition as an essential issue among young patients, reflecting an impact on everyday functioning (5, 6). However, studies concerning neurological features after COVID-19 infection in children are incoherent and heterogeneous, with few follow-up studies.

Therefore, the present study aimed to investigate neurological features after COVID-19 infection in pediatric patients treated at our tertiary center, as well as highlight the importance and raise awareness of novel coronavirus infection features.

Materials & Methods

Study design

A cross-sectional, observational survey was conducted at a single tertiary academic hospital. The department was not a primary acute pediatric COVID-19 center. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used to formulate this study (11).

Population

A retrospective chart review of all pediatric patients (age 0-18 years) who underwent neuropsychiatric evaluation for neurological symptoms after COVID-19 infection (as inpatients or outpatients care patients) during 1,5 years of the pandemic (from December 2020 through June 2022) was performed, followed by a 1-year follow-up period.

Data collection and extraction

Data included age, gender, symptoms, neurological manifestations, and symptom duration (new-onset, persistent, or relapse). The current study included patients with a history of confirmed or probable COVID-19 infection, experiencing symptoms lasting at least two months, and occurring within three months after COVID-19 infection (post-COVID-19), as well as patients with symptoms lasting 4-12 weeks (long COVID-19) (5-7, 12-13). In this study, the timely association of a previous COVID-19 infection was assessed using a real-time polymerase chain reaction (PCR) antigen test on nasopharyngeal swab samples. Additionally, positive epidemiological data, such as probable COVID-19 infection indicated by exposure to the virus through a confirmed infection in family members who show clinical symptoms, were considered. Serology tests for persistent COVID-19 antibodies were also used in the evaluation.

Exclusion criteria included neurological symptoms before COVID-19, neurological symptoms of other origin, severe acute COVID-19 infection with hypoxia, and MIS-C, and the presence of chronic illness that could have caused neurological symptoms, e.g., patients with established epilepsy who developed a recurrence of epileptic seizures were also excluded.

Endpoints and objective

The primary objective was to depict our experience with neurological features after COVID-19 in children. The secondary objective was to investigate clinical characteristics, evaluate duration and outcomes, identify risk factors, and compare findings with the literature to gain better insight and improve understanding of this long-lasting post-infectious pathology.

Data analysis and statistics

Data obtained in this study were processed using Excel (Microsoft Office 365 ProPlus, U.S.). Standard descriptive methods were used. Results were expressed as numbers and percentages for categorical variables. For continuous numerical variables, values are presented as median and minimum and maximum for non-normal distributions, as mean and standard deviation for normal distributions, and as interquartile range and total range as indicators of deviation from the median. The Kolmogorov-Smirnov test tests the normality of the distribution. Statistical significance was set at $\alpha = 0.05$. Graphical and tabular presentation methods were used. Differences in observed characteristics are assessed using the Chi-square test (χ^2 test). The analysis was performed in the statistical software STATISTICA 12, manufactured by Tibco, California.

Ethics

The use of patient medical documentation and the study design was approved by the Institutional Ethics Committee (Ethical Committee of Sestre milosrdnice University Hospital Center). The study was conducted in compliance with the ethical principles and standards of the Declaration of Helsinki 1975, revised in 1983.

Results

Eighty-four pediatric patients were included, with a median age of 12.7 years (range 0.5-18; IQR = 9.98-15.3 years). A histogram of patients' age and symptoms is shown in Figure 1. Girls were more affected than boys (female: 51; 60.7%; male: 33; 39.3%; $\chi^2 = 3.86$; $p=0,049$). Preexisting medical conditions of our patients were investigated, and none of our patients had any previous comorbidities.

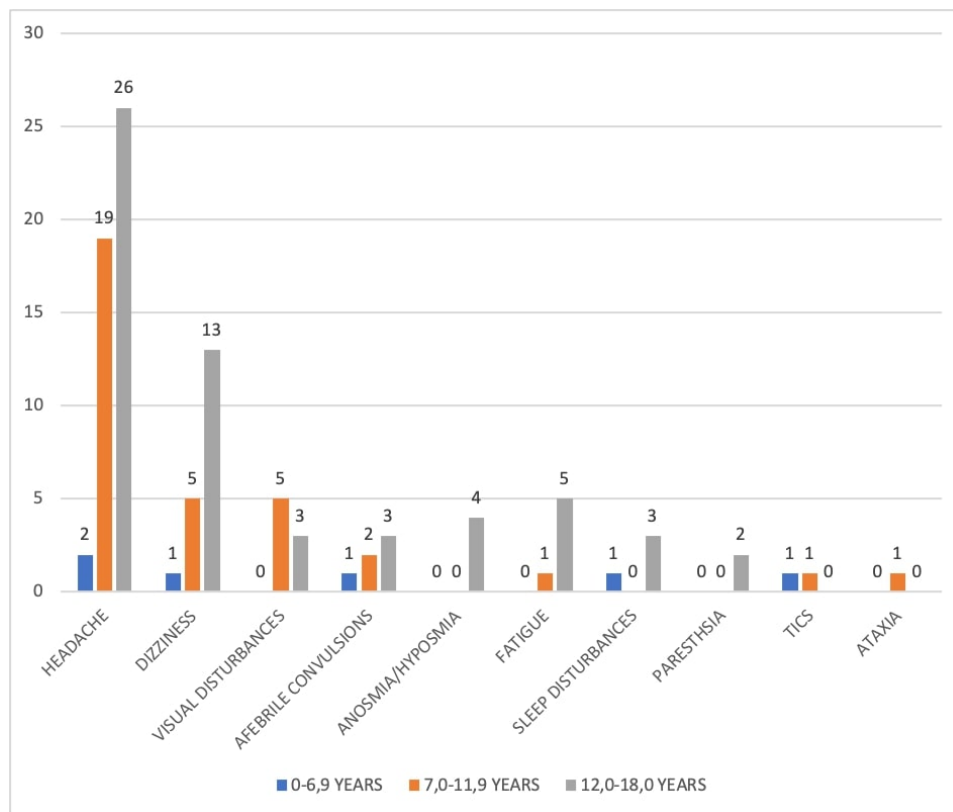


Figure 1. Neurological manifestations after COVID-19 in the studied pediatric patients of different age groups

The most common neurological manifestation in the studied patients was headache ($n = 47$; 55.9%), occurring predominantly in patients aged 12–18 years, and it was significantly more frequent in boys (1.48 times more frequent, $\chi^2 = 4.167$; $p = 0.041$). The second most common symptom was dizziness ($n = 19$; 22.6%), also predominantly in 12-18-year-old patients and 1.72 times more frequent in boys, but without a statistically significant difference ($\chi^2 = 1.83$; $p = 0.176$). Fatigue and sleep disorders occurred in 13.7% (11/84) of our patients (fatigue ($n = 6$), malaise ($n = 1$), sleep disorders/insomnia ($n = 4$)). Visual disturbances (impairment ($n = 5$) and diplopia ($n = 4$)) were present in 10.7% (9/84) of patients, primarily present in patients between 7 and 11 years of age, whereas

afebrile convulsions/seizures were present in 7.1% (6/84) of patients. Anosmia/hyposmia/dysosmia occurred in 4.7% (4/84) of patients, whereas tics occurred in 2.4% (2/84). Some patients exhibited multiple symptoms. Other symptoms (each found in one patient): increased headache/migraine frequency, lightheadedness, hair loss, facial paresis, vomiting, psychogenic episode, retrobulbar pain, tremor, myalgia, phonophobia, and photophobia. The average duration of symptoms (from the onset to the first neuropediatric examination) was three months. In total, 58.3% (49/84) of patients had symptoms lasting two months.

PCR confirmed evidence of prior COVID-19 infection in 24% of patients ($n = 20$). The most

significant number of patients with neurological symptoms after COVID-19 infection were observed between October 2020 and March 2021 (44/84; 52.4%), with the peak in December 2020 (n = 18; 21.4%).

Twenty-nine (34.5%) patients in this study had multiple (2 or more) symptoms after COVID-19, of whom 22 had headache as one of the symptoms. 4.8% (4/84) of patients were recorded as having three or more symptoms.

Patients who presented with afebrile convulsions had normal electroencephalogram and neurological assessment. Seizures without other cause occurred in 7.1% (6/84) of the studied patients, on average 3.7 (range 1-5) months after COVID-19 infection. During follow-up, four out of six patients developed another seizure; therefore, antiseizure medication was introduced. After admission, patients were followed in an outpatient clinic. Almost all children returned to baseline levels of health. In total, 22.6% (19/84) of patients required psychological support, of whom 4.8% (4/84) of patients required psychiatric consultation due to the development of a suspected mental disorder during one year of follow-up.

Discussion

Neuroinvasive potential (accessing and entering the nervous system) of coronaviruses has been described (1, 4). The neuropathophysiological mechanisms underlying the post-COVID-19 condition have been poorly understood and appear multifactorial, resulting in dysfunction of the autonomic nervous system, physical and cognitive fatigue, and changes in mood, concentration and memory (1). In children, alongside neurodevelopmental changes, sociopsychological and behavioral disturbances (school closure and social isolation) have also contributed (8, 10, 14).

Reported risk factors include female gender, older age (higher prevalence in children aged 12–17 years), preexisting medical (chronic) conditions, allergies, obesity, metabolic and immune status (5,8-9, 15). The obtained results align with the results from similar studies and show that neurological manifestations after COVID-19 infection appear more frequently in school-aged children, predominantly in female patients. The gene for ACE-2 is located on the X chromosome, which is susceptible to inactivation in females, suggesting a role for genetic variability and gender differences in COVID-19 outcomes (lower morbidity and mortality in female patients) (16). Further, it is crucial to keep in mind that older children are verbal and prone to subjectivity and bias when reporting on themselves or their studies (17). Furthermore, some authors found an association between the quantity/number of moderate or severe persistent

symptoms in exposed or infected individuals and in other household members (18).

Virus variants may contribute to presentation and sequelae, although a similar symptom profile (long-lasting symptoms) was observed in children infected with the Omicron and other variants (19). In the present study, the most significant number of patients with neurological symptoms after COVID-19 was detected before the Omicron variant, during the fifth wave in Croatia at the end of 2021 (20). Similarly, some authors reported a lower incidence of post-COVID-19 conditions among children after infection with the Omicron variant (9). However, a greater incidence of neurological symptoms (including acute ones, febrile seizures, and the like) was noted during infection with Omicron variants (1). This observation could be due to faster Omicron replication in the respiratory tract, leading to less severe disease but longer-lasting symptoms, and to fewer cases of MIS-C (9). Nonetheless, more health issues (including mental) were found in the first wave compared with the second wave (21). Thus, the obtained results implicate the possible influence of specific virus variants (pre-Omicron compared to post-Omicron variants), as well as highlight the importance of physical and mental relationships in the pediatric population. The present findings also implicate the sensitivity of the vulnerable pediatric population to sociopsychological, pandemic-related challenges, which probably attenuated the symptoms according to some authors (8). Lockdown reduced social contact, satisfactory education, physical activity, and increased isolation, as well as screen time, which are also recognized as risk factors for pervasive disorders (namely digital autism) (5). Simultaneously, anxiety and mental problems (tics, obsessive-compulsive symptoms, emotional lability, aggressiveness, and hyperactivity) were observed in children during the pandemic (1, 10, 17). In this cohort, psychological consultation and/or psychotherapy were required in 22.6% of patients, out of which four patients required psychiatric consultation due to the development of a suspected mental disorder during one year of follow-up.

Similar to adults, the neurological system was most commonly affected after COVID-19 infection in children (followed by the cardiovascular system), resulting in either specific or nonspecific symptoms such as headache and fatigue (as the most frequent), cognitive impairment (referred to as brain fog), sleep disturbances, and anosmia (5, 9, 17, 21, 23). In the current study, the most common neurological symptoms after COVID-19 infection included headaches (present in more than half of our patients), dizziness, fatigue, and sleep disorders (the last two are often difficult to distinguish). Data regarding anosmia

and sleep disturbances were in concordance with the literature (23). Sometimes symptoms occur in clusters, as seen in the obtained results, similar to chronic fatigue syndrome (myalgia syndrome) or neuropsychiatric conditions, such as post-traumatic response (1, 24, 25). Before COVID-19, these symptoms, with the exclusion of other diseases, could be reflected as a functional neurological and psychosomatic disorder. However, after COVID-19, neurocognitive and neuropsychiatric or physiological symptoms were more emphasized, whereas neurological symptoms diminished (10). Nevertheless, similar post-COVID-19 symptoms occurred in the PCR-positive and PCR-negative groups of teenagers, whereas fatigue and headache were as high in the PCR-positive group (5). Afebrile convulsions may occur after COVID-19 infection, but often appear as an acute manifestation (fever-associated seizures), specifically in cases of infection with Omicron variants, during which seizure exacerbation was also noticed in patients with active epilepsy as a high-risk population requiring careful monitoring (26, 27). Four out of six of our patients with afebrile convulsions manifested another seizure during follow-up; therefore, antiseizure medication was introduced. Although the risk of epilepsy or seizures was significantly raised after COVID-19 compared with influenza, the absolute risk remains low (affecting less than 1% of all patients with COVID-19) (28).

The present study showed that the median time span to visit a physician with neurological symptoms persisting after recovery from COVID-19 was one month, overlapping with the time window when a severe condition such as MIS-C could be expected after a COVID-19 infection, particularly in cases involving multiple organ systems. Neurological symptoms manifest in approximately half of MIS-C patients and include headache (most common), altered sensorium, seizure, muscle weakness, confusion, irritability, or behavioral changes (6, 14). Long COVID-19 has been reported to last mostly for 3-6 months, and only a few patients had symptoms lasting longer than six months (up to 12 months), suggesting that symptoms are temporary and resolve with time (1,6,10,15,17,22). The most common symptoms at three months were fatigue, behavioral changes, and sleep disturbances, whereas at six months, fatigue and headaches were the most common symptoms (19, 22, 29, 30).

The management of long COVID-19 and post-COVID-19 is undetermined, as the pathophysiology is unclear. An individual holistic approach, including support and temporary individualization of the school program, was recommended and well accepted in our experience. For instance, teachers are advised to use

concise and straightforward instructions and limit the number of tasks assigned to students at once. It is also essential for teachers to confirm students' understanding of the lesson and motivate them to ask questions if needed. Additionally, teachers should ensure that students receive all lesson materials, specifically if students were unable to take notes during class. Consistently encouraging and praising students for the effort they put into their academic tasks and responsibilities is essential for their growth and confidence. By preventing exposure to the virus, the burden of long-lasting symptoms could be reduced, yet not eliminated (9, 19). Recent studies have shown that vaccines notably reduce the risk of long COVID-19, regardless of the number of doses. It is not specified which symptoms are reduced more; however, a possible protective effect has been reported for cognitive symptoms and sleep disorders (9).

While this study has some limitations—such as being conducted at a single center, using retrospective data collection, lacking a control group, and having follow-up appointments in the post-COVID-19 neurological outpatient clinic managed by three different physicians—it nonetheless offers intriguing insights. These insights shed light on rare cases of persistent neurological symptoms in pediatric COVID-19 patients, focusing on their presentation, duration, follow-up, and management.

In Conclusion

Long-COVID-19 and post-COVID-19 symptoms, specifically neurological, have contributed to the daily limitations and morbidity in pediatric patients, presenting socioeconomic and psychological burden. Neurological post-COVID-19 symptoms require medical attention and proper management to exclude more severe conditions. Available vaccines may represent a preventive measure, particularly in school-age children where these severe conditions appear to be more common. In most patients, post-COVID-19 clinical symptoms have resolved. This pandemic additionally indicated the need for a better understanding and support for mental disorders in children.

Although more profound knowledge regarding COVID-19 pathophysiology and molecular mechanisms is required, research encourages more studies on neurological manifestations after COVID-19 in children, with the purpose of a more focused clinical approach and treatment.

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None.

Author's Contribution

Tena Trbojević contributed to study conception, conducted the data collection and wrote the manuscript. Ana Kovačević contributed to study conception, assisted with the data collection, reviewed the manuscript and prepared the paper for publication. Monika Kukuruzović, Iva Šeparović and Vanja Bašić

Kes reviewed the manuscript. Maša Malenica contributed to study conception, supervised the entire conduct of the study and reviewed the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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