Post-Acute COVID-19 Syndrome in a 17-Year-Old: A Wolf in Sheep's Clothing

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Abstract

Two years into these pandemic several complications of COVID-19 are still insufficiently understood, especially in children.

A 17-year-old girl presented to the pulmonary out-patient clinic primarily with shortness of breath, but additional neuromuscular and neurocognitive impairment as well as persistent headaches two month after an acute SARS-CoV-2 infection.

Pulmonary function test showed massive restriction (FCV 40%), but normal diffusion capacity of CO and lung clearance index. Further extensive diagnostic work-up revealed muscular impairment and peripheral neuropathy in the lower extremities of para-infectious origin. Clinical symptoms regressed rapidly after a 5-day course of Methylprednisolone. The patient remained asymptomatic after rehabilitation treatment.

Keywords: COVID-19 • Infectious disease • Neuropathology • Pediatrics • Respiratory disorder

Abbreviations: DLCO: Diffusion Capacity of CO; FeNO: Fraction Exspiratory Nitric Oxide; FEV1: Forced Expiratory Volume in 1 Second; FVC: Forced Vital Capacity; HR: Heart Rate; LCI: Lung Clearance Index; MIP: Maximum Inspiratory Pressure; SpO_2: Saturation of Peripheral Oxygen

Introduction

In the second year of this pandemic several complications of COVID-19 are still insufficiently understood, especially in children. However, clinicians became aware, that pediatric patients with even mild COVID-19 symptoms are at risk to develop long-lasting deficits [1,2]. Even though the clinical picture of acute infection has its focus mainly on the respiratory and cardiovascular system, Central and Peripheral Nervous System (CNS and PNS) complications become increasingly apparent [3].

Authors monitoring acute and long-term neurologic complications of SARS-CoV-2 infections in children correctly emphasize the importance of being more vigilant to para-infectious conditions in children, which are still under-recognized [4,5].

Case Presentation

We present the case of a 17-year-old girl with severe post-acute COVID-19 symptoms. The patient was referred to our pulmonary out-patient clinic two months after positive testing for SARS-CoV-2. The patient had confirmed contact to SARS-CoV-2 in the middle of February 2021 with a negative Polymerase Chain Reaction (PCR) test at day one after contact. At day two after contact first symptoms became apparent with loss of smell and taste, as well as slight cough, shortness of breath, myalgia, and abdominal pain. The patient was first-ever tested positive by PCR test (initial CT value of 19) seven days after confirmed SARS-CoV-2 contact, therefore self-isolation at home was mandated. The parents described progressive circulatory and concentration disturbances in her daughter. The patient was mainly confined to bed, experienced difficulties to focus on conversations and showed signs of dysphasia. Due to loss in appetite the patient lost 9.4% of her body weight.

One month later the patient was first tested negative for SARS-CoV-2 accompanied by a slight improvement of clinical symptoms. About two weeks later, there was a second impressive onset of symptoms with chills and fever, myalgia, recurring vomiting, headaches, and neurocognitive deficits. Furthermore, there were episodes of hyperaesthesia in both upper extremities and muscular weakness in both legs. The patient was unable to walk more than a few steps on her own, therefore, great physical support was necessary by her family members. She was completely unable to climb stairs on her own.

First examination in our out-patient clinic revealed shallow breathing, equally ventilated lungs with reduced breathing sounds on auscultation and no clinical signs of dyspnoea or obstruction. Vital parameters were stable with an oxygen saturation of 100%, but the heart rate was elevated with 120 beats/min. Lung function testing showed signs of pulmonal restriction (FCV reduced to 40%, Table 1) with no evidence for airway inflammation or peripheral lung dysfunction in Diffusion Capacity of CO (DLCO) and Lung Clearance Index (LCI). Repeated testing showed increasing restriction most likely due to physical exhaustion. We immediately initiated hospitalization for further diagnostics and medical care for our patient.

Table 1. Pulmonary function testing.

Days since diagnosis (days)	FEV1 (%)	FVC (%)	FEV1/ FVC (%)	LCI	DLCO (%)	FeNO (ppB)	MIP (%)	6MWT			
								Distance (m)	Borg's scale, max.	SpO_2, lowest (%)	HR, max. (min^{-1})
58	45	40	113	6.31	91	5					
	32	42	84								
In-patient care								**Wearing a surgical mask**			
65	46	47	97					110	10	96	130
66							66				
Methylprednisolone 1 g/d over 5 days								**Wearing FFP2 mask**			
71								550	0	95	137
72	95	90	104								
							96				
Out-patient follow-up											
87	100	106	93	6.9	87						

Note: DLCO: Diffusion Capacity of CO; FeNO: Fraction exspiratory Nitric Oxide; FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; HR: Heart Rate; LCI: Lung Clearance Index; MIP: Maximum Inspiratory Pressure; SpO2: Saturation of Peripheral Oxygen

At first presentation and at hospitalisation there was no evidence for Pediatric Inflammatory Multisystem Syndrome (PIMS) [6]. There was no persistent fever, no signs of systemic inflammation (like neutrophilia, elevated CRP and lymphopenia). Besides severe pulmonary restriction there was no evidence of multi-organ dysfunction such as shock, cardiac, renal, gastrointestinal, or acute neurological disorder.

Lung function testing at hospitalisation showed persistent findings (Table 1). A 6-Minute Walk Test (6MWT) was discontinued by the patient at 5 min 40 sec because of severe subjective dyspnoea (Borg's scale 10/10, distance 105 m). A Computed Tomography (CT) of the chest showed no signs of structural pulmonary changes or pulmonary infiltrates. Function testing of the respiratory muscles showed slightly elevated strain (Table 1). Continuous monitoring of the patient revealed no signs of nightly hypopnea, apnoea, hypoxia, or hypercapnia. Examination by a pediatric cardiologist shortly before hospitalization was normal.

On further neuropediatric examination, the patient showed normal findings for vigilance, orientation, cranial nerve function, pupillometry and pursuit eye movements and no somatosensoric deficit on all four extremities. Electroencephalography (EEG) was normal as well. Muscles were normotonic and eutrophic bilaterally, muscle strength was of grade 4-5 of 5 in all four extremities. The pyramidal drift test was pathological in the right arm. Toe and heel walking, Romberg's test and Unterberg's test were impossible. Cognitive testing revealed slight difficulties in working memory, especially long-time memory and recall of task information. All other cognitive areas were within normal limits.

Muscular ultrasound was performed in the bilateral biceps brachii, brachioradialis, quadriceps femoris and tibialis anterior muscle and was graded using the Heckmatt Score (HS) [7,8]. Muscular ultrasound assessment showed normal HS results in both upper extremity muscles (grade 1). In the lower extremities the bilateral quadriceps femoris and tibialis anterior muscles showed a slight increase of echointensity and slightly altered structure of the muscles (grade 2) in the HS.

Neurosonography showed light inflammatory alteration of the right N. peroneus R. profundus in the means of long stretched, fascicular-accentuated swelling with preserved echo structure and a cross sectional area of 0.07 cm^2 distal the head of the fibula versus 0.04 cm^2 at the middle lower leg.

Cranial Magnetic Resonance Imaging (MRI) and lumbar puncture were performed to rule out Guillain-Barré Syndrome (GBS) or post-COVID encephalopathy. Cranial and spinal MRI showed no signs of chronic demyelinating or other inflammatory processes, no brain tumor or cerebral atrophy. Cerebrospinal Fluid (CSF) examination was without evidence for acute or chronic inflammatory diseases. Microbiological examinations for viral and bacterial pathogens in CSF as well as blood were negative. Immunologic diagnostics of blood and CSF only revealed slightly elevated sulfatide-IgM-antibodies in the CSF. COVID-19 antibodies in the CSF were negative.

Electrophysiological examination presented no signs of decrement or myasthenic reaction. Furthermore, Nerve Conduction Velocity (NCV) gave evidence of axonal impairment in the sensitive nerve tract of N. peroneus superficialis and N. suralis on the left side. Motor NCV revealed a reduction in left N. peroneus as well as prolonged F-wave latency, and motor NVC reduction in Nn. tibialis bilaterally with discrete prolonged F-wave latency. In conclusion, leg-accentuated axonal neuropathic impairment was suspected. While Motor-Evoked Potentials (MEPs) showed normal findings, suspicion was amplified by Sensory Evoked Potentials (SEPs) with borderline prolonged P40-latency on the right side in addition to reduced amplitude and slightly deconfigured potentials suggesting axonal impairment of the somatosensory tract in the right leg.

In summary of all clinical and diagnostic test results, we suspected a para-infectious leg-accentuated atactic-sensory neuropathy due to COVID-19. Additionally, the suspected involvement of the respiratory muscles might have caused the shortness of breath, that appeared as pulmonary restriction and reduced Maximum Inspiratory Pressure (MIP).

Based on an interdisciplinary decision, we started a treatment approach with methylprednisolone 1 g per day over five days. In addition, the patient received daily physiotherapy, including breathing guidance. The patient was counselled by a psychologist and a dietary adviser concerning nutrition at persisting loss of appetite.

Therapy was well tolerated and showed prompt improvement in all relevant areas (Table 1). After nine days the patient was discharged from hospital and into out-patient rehabilitation. The follow-up examinations in our out-patient clinic (two weeks and three months after discharge) gave no evidence for remaining clinical symptoms.

Discussion

The patient presented a variety of prolonged and recurring symptoms two months after SARS-CoV-2 infection. Although the patient received ambulatory treatment in the acute phase of COVID-19, hospitalization might have been indicated earlier. Finally, the diagnosis in this patient was challenging as the pulmonary symptoms seemed to be leading.

Further extensive interdisciplinary examinations led to neurological and neuromuscular complications associated with COVID-19. While pulmonary CT, DLCO und LCI were normal, severe restriction and reduced MIPs were most likely associated with neuromuscular involvement. Reduced strength in all extremities, pathological pyramidal drift test in the right arm and impossibility to perform walking tests were obvious clinical signs. Neuromuscular sonography findings gave evidence for paresis in the lower extremities.

Exclusively, sulfatide-IgM-antibodies were detected in the CSF. Sulfatides are the main component of the acidic glycosphingolipids and thus a surface component of the myelin sheath in the peripheral and central nervous system. The detection or temporary elevation of sulfatide antibodies especially of the IgM antibody subclass was described in chronic infections or autoimmune diseases, especially in chronic ataxic-sensory neuropathy [9]. A cross reaction with MAG antibodies could be ruled out since there was no evidence of monoclonal gammopathy in this case. Incidentally there was in selective IgA deficiency, which is correlated with higher risk of severe COVID-19 and associated complications such as cytokine storm syndrome, autoimmune conditions like Guillain-Barré Syndrome (GBS) [10]. Considering that, sulfatide-antibodies were found in the CSF but not in the blood, the course of the disease was estimated as mild. Thus, a single course of methylprednisolone pulse therapy for five days seemed reasonable. Because symptoms were rapidly and almost completely regressive under methylprednisolone, we abstained from long-term or pulsatile cortisone treatment [11].

Certainly, long-term confinement in bed and weight-loss of 9.4% during the acute phase of SARS-CoV-2 infection may have caused moderate myatrophy, and probably contributed to the severely reduced condition at the time of hospitalization. Perceptible improvement of dyspnoea and pulmonary restriction under physiotherapeutic training is also an indication for that.

In 2020 Ludvigsson first described a case study of five Swedish children (median age 12 years) with prolonged symptoms after COVID-19, including mostly fatigue, dyspnoea, heart palpitations or chest pain, but also headaches, difficulties of concentrating, muscle weakness, and dizziness. The systemic review in November 2020 revealed that no publication so far contained any information on long COVID in children [12]. Following studies in different countries confirmed post-COVID symptoms even in asymptomatic children, and persisting neurological and neuromuscular symptoms [13,14]. Unfortunately, no further neuropediatric diagnostics were described in these studies.

More severe neurological symptoms or syndromes are often described in ICU COVID patients with acute cerebrovascular disease, polyradiculoneuritis like GBS, peripheral neuropathies, and others [15,16]. It is uncertain to which extend these are caused by acute infection, para or post-infectious inflammatory disorders or complications of critical illness. Yet, case studies with analysis of CSF in SARS-CoV-2 patients with neurological symptoms suggests most likely secondary immune phenomena such as autoimmune mediated hyperinflammatory processes. Findings of sulfatide-antibodies in our case confirmed the pathomechanism and we chose methylprednisolone therapy since good clinical response is well-documented in these kind of cases. An investigation on neuroinvasive and neurotropic human respiratory Coronaviruses by Desforges, et al. in 2014 using data from animal trials states that “neurological disease appears partially immune-mediated and may result in uncontrolled secretion of cytokines that leads to diverse pathological manifestations (…) even spinal cord involvement” [17]. While pathomechanisms are still under broad investigations, the virus is rarely found in CSF [18]. More commonly anti-neuronal or anti-glial autoantibodies are found like in our patient.

Nevertheless, neurological approach of acute SARS-CoV-2 infection and post/long-COVID is still in progress and rare post-infectious conditions like in our patient are hardly recognized. A Romanian case study in a few patients with residual symptoms (myalgia, generalized or at lower extremities, fatigue and exhaustion under stress) after mild COVID-19 showed signs of demyelinating polyneuropathy [20]. There is no information on further approach or treatment. Thus, despite in our case there were no signs of demyelisation, post or para-infections neuropathy in the lower extremities seems to be not as unlikely as expected, although it might be hard to detect in a multisymptomatic post-COVID patient.

Conclusion

In patients with acute or post-COVID primary symptoms like shortness of breath, general weakness and cognitive difficulties may disguise underlying para or post-infectious neurological impairment. An interdisciplinary approach is recommended, and para-infectious pathologies should be taken in consideration. There is an urgent need for further investigations of long-term effects of SARS-CoV-2 in children and how it will affect general and pediatric health care in the future.

Consent for Publication

Written consent is available upon request.

Competing Interests

The authors declare that they have no competing interests.

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