



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

SARS-CoV-2 related paediatric acute-onset neuropsychiatric syndrome

COVID-19 might be asymptomatic or might present with various signs and symptoms, such as a non-productive cough, fever, myalgia, fatigue, malaise, and gastrointestinal disturbances. Neurological and psychiatric disorders in patients with a COVID-19 infection have been reported, such as cerebral ischaemic stroke, intracerebral haemorrhages, encephalopathy, and cerebral vasculitis.¹ The peripheral nervous system might be also affected. Ageusia, anosmia, myalgia, paraesthesia, and Guillain-Barré syndrome are the most reported disorders affecting the peripheral nervous system in patients with COVID-19.^{2,3}

Post-infectious, autoimmune, and neuro-inflammatory events are the main mechanisms of paediatric acute-onset neuropsychiatric syndrome (PANS).⁴ PANS presents with a sudden onset of obsessive-compulsive disorder (OCD) or a severely restricted food intake, and concurrent neuropsychiatric symptoms and motor dysfunction.⁴ The estimated prevalence of OCD in childhood and adolescence is 0.25–4.00%, with those aged between 16–18 years (1%) having the highest prevalence.^{5–7} Here, we report on two unrelated children with PANS that started 2 weeks after a positive COVID-19 nasopharyngeal swab.

Patient one was a 12-year-old boy referred to our Paediatric Clinics Department (Azienda Ospedaliera Universitaria Policlinico) for an abrupt onset of psychiatric disturbances. No movement disorders or neuropsychiatric disturbances were previously reported in his medical history nor in his family. Because of cases of COVID-19 among his classmates, a screening for SARS-CoV-2 by nasal swab (RT-PCR) was

done at the patient's school. That screening found that the patient was positive for SARS-CoV-2. As reported by his parents, initially the child did not show any symptoms.

After approximately 2 weeks, the boy presented a sudden onset of psychiatric signs, such as a fear of catching infections and touching handles with a severe drive to wash his hands very often and accurately. Moreover, in this period, he showed a reduced appetite. A general physical examination showed that he was physically healthy, including cardiac and neurological examinations. In the meantime, severe emotional lability and facial motor tics were reported by his parents and observed during our examination. Routine laboratory examinations were normal, including an anti-streptolysin O titre of 198 IU/mL (healthy values, <250 IU/mL); anti-DNAse B (antibodies against deoxyribonuclease B of the group A *Streptococci*) of 101 IU/mL (healthy values, 0–200 IU/mL); and anti-basal ganglia antibodies with a titre of 1:200 (healthy value, absent). An autoimmunity panel, including anti-endomysium antibodies, anti-extractable nuclear antigens antibodies, anti-nuclear antigens antibodies, anti-mitochondrial antibodies, anti-smooth muscle antibodies, and serological study for main infectious agents, such as *Mycoplasma pneumoniae*, Rubella virus, Epstein-Barr virus, cytomegalovirus, *Chlamydia pneumoniae*, herpes simplex virus 1 and 2, and *Toxoplasma gondii* were normal. At admission to the hospital, a new nasal swab for SARS-CoV-2 was done and was positive, 14 days after the first positive test. The results of the electroencephalogram (EEG) and electrocardiogram (ECG) were normal, as were those of the brain MRI (appendix p 2). The Children's Yale-Brown Obsessive-Compulsive Scale⁸ score was 22 (appendix p 1). A score of more than 16 is generally considered indicative of the presence of OCD (16–23=moderate severity; 24–40=severe). Psychological

intervention was advised and rapidly started.

After 2 months of follow-up, his distress for hand cleanliness persisted along with selective eating. Motor tics also persisted but were not constantly present. A swab test for COVID-19 was negative. The mother of the patient still had complaints about the boy's lack of attention and irregular writing.

Patient two, a 13-year-old boy, was admitted at the Paediatric Department (Azienda Ospedaliera Universitaria Policlinico) because of the sudden onset of psychiatric symptoms, such as a compulsive disorder characterised by using only a tablespoon during his meals and arranging the tip of his shoes in parallel before going to sleep. His parents denied noticing the presence of these symptoms previously. 13 days before admission to the hospital, the boy complained of a fever, cough, cutaneous rash, and gastrointestinal disturbances. Therefore, he underwent a nasopharyngeal swab for SARS-CoV-2 and was diagnosed with COVID-19. At the physical and psychological examination, he had a facial motor tic, guttural vocal tics, hyperactivity, aggressiveness, irritability, inattentiveness, and inappetence. Laboratory blood testing produced normal results. He underwent a pharyngeal swab for bacteria culture, an anti-streptolysin O test and anti-deoxyribonuclease titre, and an autoimmunity panel including anti-endomysium antibodies, anti-extractable nuclear antigens antibodies, anti-nuclear antigens antibodies, anti-mitochondrial antibodies, anti-smooth muscle antibodies, anti-basal ganglia antibodies, and serological studies for *M pneumoniae*, Rubella virus, Epstein-Barr virus, cytomegalovirus, *C pneumoniae*, herpes simplex virus 1 and 2, and *T gondii*. He also underwent a nasopharyngeal swab for SARS-CoV-2. All tests had either negative or normal results except for anti-basal ganglia antibodies, which had a titre of 1:100 result (appendix p 1). EEG and ECG yielded normal results, as did



Published Online
May 4, 2021
[https://doi.org/10.1016/S2352-4642\(21\)00135-8](https://doi.org/10.1016/S2352-4642(21)00135-8)

See Online for appendix

a brain MRI. The Children's Yale-Brown Obsessive-Compulsive Scale score was 28.⁸ Psychological treatment was started. After 1 month, no relevant clinical modification was noted. The parents reported that the boy was still more aggressive and more irritable than in the past.

The two young adolescents here reported had a clinical diagnosis of new-onset PANS. Both were previously diagnosed with COVID-19 by a nasal swab. PANS is a disorder affecting children and adolescents, of which the onset is characterised by a sudden development of neurological and psychiatric symptoms following infection.⁹ No specific diagnostic biomarker has been recognised for this disorder, but an infectious and autoimmune mechanism has been proposed in most cases.¹⁰ Neurological manifestations of COVID-19 have been widely reported, mainly affecting adults. Varatharaj and colleagues,¹¹ in a UK-wide surveillance study on 153 patients, for which complete datasets were available for 125/153 (82%) patients, reported cerebrovascular events in 77/125 (62%) patients, ischemic stroke in 57/125 (46%) patients, intracerebral haemorrhages in 9/125 (7%) patients, and CNS vasculitis in a single case (1/125; 0%). Peripheral nerve disorders, including altered smell and taste dysfunction,^{12,13} Guillain-Barré syndrome,¹⁴ and muscle damage¹⁵ were also reported and ascribed to a SARS-CoV-2 infection. A descriptive study was done in 130 children¹⁶ with confirmed diagnosis of COVID-19 by 28 centres in 10 regions in Italy. Among all signs and symptoms, those that could be grouped as neurological included hyporeactivity (somnolence) or hyperactivity (excessive crying) 4/130 (3.0%), febrile seizures 2/130 (1.5%), and pain in lower limbs 1/130 (0.7%). In a review of the neurological manifestations presented by patients with COVID-19, Niazkar and colleagues² noted that both the CNS and peripheral nervous system might be affected, the most frequent symptom being headaches.

Clinical manifestations included dizziness, impaired consciousness, acute cerebrovascular disease, epilepsy, ataxia, acute disseminated encephalomyelitis, and viral encephalitis.² Disorders affecting the peripheral nervous system were less severe and included hyposmia or anosmia, hypogeusia or ageusia, muscle pain, and Guillain-Barré syndrome.²

Neurological manifestations of COVID-19 have been described in patients of all ages but are usually less severe in childhood.¹⁷ Encephalopathy was reported by Nathan and colleagues¹⁸ in four infants and in a toddler with COVID-19. In the infants, the clinical manifestations were axial hypotonia, drowsiness, and moaning sounds.¹⁸ The course was benign with a rapid clinical improvement a few days after admission. In all patients, a nasal swab for COVID-19 was positive and, remarkably, cell counts, glucose, and PCR for SARS-CoV-2 in cerebrospinal fluid were negative. Lin and colleagues¹⁹ reported 82 children and adolescents who were admitted to hospital with laboratory-confirmed COVID-19, of which 35/82 (43%) developed neurological symptoms. The clinical symptoms included headache, 12/82 (34%); fatigue or malaise, 9/82 (25%); altered mental status, 8/82 (23%); weakness, 5/82 (14%); and epileptic seizures, 4/82 (11%). Three children had cranial sixth nerve palsy, which in two of them was linked to intracranial hypertension. Stroke was reported only in one child, and two children had dysgeusia or ageusia. Among 10 patients whose cerebrospinal fluid was tested for SARS-CoV-2 by RT-PCR, no viral RNA was found.

Our two cases show a temporal correlation between COVID-19 and the onset of PANS. Therefore, it is possible that, in these cases, the SARS-CoV-2 virus has caused PANS, although this cannot be confirmed. PANS belongs to a group of neurological disorders suspected to have a post-infectious origin.²⁰ Paediatric autoimmune neuropsychiatric disorder

associated with streptococcal infection (PANDAS) also belongs to this group.²¹ PANS and paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection share many signs and symptoms, and an acute and sudden onset.⁴ These two disorders also seem to have a common autoimmune and neuro-inflammatory pathogenesis, although no specific markers have still been found and the disorders have also been linked to several events, including toxic, endocrine, and metabolic dysfunctions.⁴

How COVID-19 can cause a neurological impairment in affected children is a debated, but unresolved, question. Lin and colleagues¹⁹ have advanced some hypotheses. First, they hypothesised a direct viral injury to neural cells through olfactory nerves and its transit to the CNS via the cribriform plate. The second hypothesis is that SARS-CoV-2 causes vascular endothelial injury through its interaction with angiotensin-converting enzyme 2 receptors. The third and final hypothesis is that COVID-19 causes an inflammatory and autoimmune injury. As a matter of fact, COVID-19 correlates, in its most serious manifestations, with aberrant and excessive inflammation mediated by innate and adaptive immune activation.²²

Here, we examined two adolescents who acutely developed new OCD, neuropsychiatric, and motor dysfunction symptoms consistent with PANS 2 weeks after a diagnosis of COVID-19. SARS-CoV-2 needs to be acknowledged in the differential diagnosis of PANS.

We declare no competing interests.

*Piero Pavone, Manuela Ceccarelli, Silvia Marino, Daniela Caruso, Raffaele Falsaperla, Massimiliano Berretta, *Emmanuele Venanzi Rullo, Giuseppe Nunnari*
emmanuele.venanzirullo@unime.it

Section of Paediatrics and Child Neuropsychiatry, Department of Clinical and Experimental Medicine

- (PP), Unit of Infectious Diseases, Department of Clinical and Experimental Medicine (MC), Unit of Paediatrics and Paediatric Emergency, Paediatric COVID-19 Centre, Azienda Ospedaliera Universitaria Policlinico, Presidio Ospedaliero San Marco (SM), Postgraduate Training Programme in Paediatrics, Department of Clinical and Experimental Medicine (DC), and Neonatal Intensive Care Unit, Neonatal COVID-19 Centre, Azienda Ospedaliera Universitaria Policlinico, Presidio Ospedaliero San Marco (RF), University of Catania, Catania, Italy; Department of Biomedical, Dental, Morphological and Functional Imaging Sciences (MC), and Department of Clinical and Experimental Medicine (MB, EVR, GN), Unit of Infectious Diseases, University of Messina, Messina 98124, Italy
- 1 Ariapooran S, Khezeli M. Symptoms of anxiety disorders in Iranian adolescents with hearing loss during the COVID-19 pandemic. *BMC Psychiatry* 2021; **21**: 114.
 - 2 Niazkar HR, Zibaee B, Nasimi A, Bahri N. The neurological manifestations of COVID-19: a review article. *Neural Sci* 2020; **41**: 1667–71.
 - 3 Sachdev K, Agrawal S, Ish P, Gupta N, Raheja K. Neurological manifestations of COVID-19: a brief review. *Indian J Med Res* 2020; **152**: 41–47.
 - 4 Gamucci A, Uccella S, Sciarretta L, et al. PANDAS and PANS: clinical, neuropsychological, and biological characterization of a monocentric series of patients and proposal for a diagnostic protocol. *J Child Adolesc Psychopharmacol* 2019; **29**: 305–12.
 - 5 Krebs G, Heyman I. Obsessive-compulsive disorder in children and adolescents. *Arch Dis Child* 2015; **100**: 495–99.
 - 6 Ruscio AM, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Mol Psychiatry* 2010; **15**: 53–63.
 - 7 Heyman I, Fombonne E, Simmons H, Ford T, Meltzer H, Goodman R. Prevalence of obsessive-compulsive disorder in the British nationwide survey of child mental health. *Br J Psychiatry* 2001; **179**: 324–29.
 - 8 Saad LO, do Rosario MC, Cesar RC, et al. The child behavior checklist-obsessive-compulsive subscale detects severe psychopathology and behavioral problems among school-aged children. *J Child Adolesc Psychopharmacol* 2017; **27**: 342–48.
 - 9 Silverman M, Frankovich J, Nguyen E, et al. Psychotic symptoms in youth with Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) may reflect syndrome severity and heterogeneity. *J Psychiatr Res* 2019; **110**: 93–102.
 - 10 Frankovich J, Thienemann M, Rana S, Chang K. Five youth with pediatric acute-onset neuropsychiatric syndrome of differing etiologies. *J Child Adolesc Psychopharmacol* 2015; **25**: 31–37.
 - 11 Varatharaj A, Thomas N, Ellul MA, et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. *Lancet Psychiatry* 2020; **7**: 875–82.
 - 12 Yan CH, Faraji F, Prajapati DP, Boone CE, DeConde AS. Association of chemosensory dysfunction and COVID-19 in patients presenting with influenza-like symptoms. *Int Forum Allergy Rhinol* 2020; **10**: 806–13.
 - 13 Bagheri SH, Asghari A, Farhadi M, et al. Coincidence of COVID-19 epidemic and olfactory dysfunction outbreak in Iran. *Med J Islam Repub Iran* 2020; **34**: 62.
 - 14 Ahmad I, Rathore FA. Neurological manifestations and complications of COVID-19: a literature review. *J Clin Neurosci* 2020; **77**: 8–12.
 - 15 Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020; **77**: 683–90.
 - 16 Parri N, Magistà AM, Marchetti F, et al. Characteristic of COVID-19 infection in pediatric patients: early findings from two Italian Pediatric Research Networks. *Eur J Pediatr* 2020; **179**: 1315–23.
 - 17 Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. *Pediatrics* 2020; **145**: e20200702.
 - 18 Nathan N, Prevost B, Corvol H. Atypical presentation of COVID-19 in young infants. *Lancet* 2020; **395**: 1481.
 - 19 Lin JE, Asfour A, Sewell TB, et al. Neurological issues in children with COVID-19. *Neurosci Lett* 2021; **743**: 135567.
 - 20 Swedo SE, Leckman JF, Rose NR. From research subgroup to clinical syndrome: modifying the PANDAS Criteria to describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome). *Pediatr Therapeut* 2012; **2**: 2.
 - 21 Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry* 1998; **155**: 264–71.
 - 22 Kakodkar P, Kaka N, Baig MN. A comprehensive literature review on the clinical presentation, and management of the pandemic coronavirus disease 2019 (COVID-19). *Cureus* 2020; **12**: e7560.