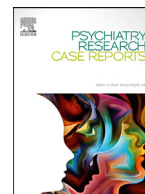




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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/COVID-19 associated pediatric acute-onset neuropsychiatric syndrome a case report of female twin adolescents

Ayşegül Efe

Department of Child and Adolescent Psychiatry, Dr. Sami Ulus Maternity, Children's Health and Diseases Training and Research Hospital, University of Health Sciences, Ankara, Turkey



ARTICLE INFO

Keywords:

Pediatric acute-onset neuropsychiatric syndrome
PANS
COVID-19
SARS-CoV-2

ABSTRACT

“Pediatric acute-onset neuropsychiatric syndrome”, or PANS, is a rare syndrome characterized by an acute onset of obsessive-compulsive disorder (OCD), and/or severely restricted food intake accompanied by a variety of neuropsychiatric symptoms. To our knowledge, this is the first case report of twin adolescents with COVID-19-associated PANS. Dizygotic twin sisters in late teens, with abrupt and acute onset of severely restrictive food intake, weight loss, OCD, anxiety with intermittent auditory and visual hallucinations, depression, attention deficit, and sleep disturbances, simultaneously accompanied by milder neurologic symptoms such as hand tremor, tinnitus, dizziness, headache, and weakness of proximal muscles, were applied to child and adolescent psychiatry clinic. The only relevant agent underlying those neuropsychiatric and somatic complaints was COVID-19, and it was validated with laboratory testing, such as positive IgG titers of SARS-CoV-2 and negative biomarkers for other possible bacterial or viral agents. Generalized epileptic anomaly and a vermian/foveal atrophy in the cerebellum were detected in further evaluations. Treatment options consisted of psychotropic agents, antibiotics, antiepileptic, and intravenous immunoglobulin transfusion finely treated the neuropsychiatric symptoms. Clinicians should consider SARS-CoV-2 as a potential agent, when a child presents with abrupt onset, dramatic neuropsychiatric symptoms also consisting of PANS, even in asymptomatic patients or with mild respiratory symptoms.

1. Introduction

Pediatric acute-onset neuropsychiatric syndrome (PANS) is an ‘exclusion’ diagnosis, with an abrupt and dramatic onset of an obsessive-compulsive disorder (OCD), and/or a severely restricted food intake which is accompanied by at least two of those following conditions, consisting of an extensive series of concurrent neuropsychiatric symptoms such as anxiety; emotional lability and/or depression; irritability, aggression and/or severely oppositional behaviors; behavioral/developmental regression; decline in academic/school performance due to deficit in attention and/or memory; sensory and/or motor movement abnormalities; somatic symptoms like sleep disturbances, impaired urinary frequency, or enuresis (Swedo et al. 2012; Thienemann et al. 2017). All these symptoms should not be explained by any other known medical or neurological conditions such as Sydenham Chorea, lupus, etc. The sudden and simultaneous onset of psychiatric symptoms, accompanied by neurologic disturbances in a variety of different severities, makes it possible to differentiate from other neurodevelopmental disorders of childhood, despite to multiplicity of overlap-

ping symptoms (Chang et al. 2015). Therefore, being in prior suspicion of the diagnosis, obtaining a complete medical and psychiatric history, as well as carrying out an exact physical examination and validation with laboratory tests, are all important for clinicians to diagnose PANS (Chang et al. 2015).

A common, multiple post-infectious immune-mediated etiology, ranging from autoimmune/auto-inflammatory disorders to recurrent infections and immunodeficiency syndromes, is suggested for PANS (Chang et al. 2015; Hesselmark and Bejerot 2019). A growing number of evidence, supporting the hypothesis of the close association between PANS/PANDAS and a variety of infections, has been accumulated over the past two decades (Hoekstra et al. 2005; Murphy and Pichichero 2002). A group of viral or bacterial agents such as *varicella*, *influenza*, *Epstein-Barr*, *Streptococcus pyogenes*, *Group A B-hemolytic streptococcus (GAS)*, *Mycoplasma pneumoniae*, and *Borellia burgdorferi* was defined for the etiology (Allen et al. 1995; Susan E. Swedo et al. 1998). However, these infection-related psychiatric syndromes are presumed to cause also by a variety of disease mechanisms with multiple etiologies such as neuro-inflammatory, toxic, metabolic (e.g., leaky gut syn-

Abbreviations: PANS, Pediatric acute-onset neuropsychiatric syndrome; PANDAS, Pediatric autoimmune neuropsychiatric syndrome associated with streptococcal infections; OCD, Obsessive-compulsive disorder; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; COVID-19, Highly contagious coronavirus disease 2019; GAS, Group A B-hemolytic streptococcus; CNS, Central nervous system; IgG, Immunoglobulin G; IVIG, Intravenous immunoglobulin.

E-mail address: aysegulboreas@gmail.com

<https://doi.org/10.1016/j.psycr.2022.100074>

Received 20 August 2022; Received in revised form 11 October 2022; Accepted 13 October 2022

2773-0212/© 2022 The Author. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

drome), or endocrine disorders, via triggering autoimmune responses (Clapp et al. 2017; Molina and Shoenfeld 2005; Zibordi et al. 2018).

A novel coronavirus termed 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2), and relevant disease now known as 'highly contagious coronavirus disease 2019' (COVID-19) causing a multiplicity of symptoms holding different systems of the body, now poses the biggest threat to infection-related syndromes, given that its pandemic has affected a large proportion of the world's population. However, relatively little is known about its potential direct impacts on mental health, despite growing recognition of the psychiatric and neurological implications of disease (World Health Organization 2020). Preliminary data suggest that patients with COVID-19 might exhibit delirium, confusion, agitation, and altered consciousness, as well as depression, anxiety, and sleep disturbances. As if considering the psychiatric burden in both acute and longer post-illness stages, being experienced in previous coronavirus epidemics, the clinicians should be vigilant to the contingency of high incidences of psychiatric disorders in the longer term.

Neuropsychiatric consequences can arise either through direct effects of infection of CNS or indirectly via host immune response or medical therapy. According to the reports of a case series from Wuhan, 36% of clients admitted to the hospital with COVID-19 presented with neurologic symptoms which mostly consisted of mild symptoms such as dizziness and headache, and only some of them had an acute cerebrovascular disease or impaired consciousness as part of their systemic illness (Mao et al. 2020). Even if severe neuropsychiatric consequences are proportionately rare, a considerable number of individuals worldwide would be affected (Troyer et al. 2020). Some plausible theories such as the direct neuroinvasive ability of SARS-CoV-2 (as well as SARS-CoV-1), hypercytokinemia/cytokine storm syndrome associated with neurologic holdings, and/or triggered autoimmunity against neuronal antigens discourse used in terms of COVID-19 associated neuropsychiatric disturbances, despite to little evidence yet.

The diagnosis of PANS is still under debate and not well defined. Therefore, it is important to better understand the pathogenic mechanisms of PANS and to identify disease-specific biomarkers (Wilbur et al. 2018). Given the severe and devastating nature of symptoms and the effects on family and children, the understanding of the biological basis and infectious agents in the background of this syndrome and the identification of evidence-based and effective therapies are necessary. This case report aims to recognize the first cases of SARS-CoV-2/COVID-19 associated PANS, who are dizygotic twin female adolescents, and to contribute to the literature concerning neuropsychiatric consequences of SARS-CoV-2 infection in the pediatric population.

2. Case presentation

Dizygotic twin sisters in their late teens were consulted to the outpatient clinic of child and adolescent psychiatry (November 2020) with acute onset, severe and simultaneous restrictive food intake, and obsessive-compulsive disorder, starting 2 months ago that was abruptly exhibited after a couple of weeks of asymptomatic SARS-CoV-2 infection. Their complaints consisted of a sense of distaste for foods, intermittent vomiting, restrictive food intake, and weight loss (average 6-8 kg in two months, decrease of BMI from 19-20 to 17), and started with an interval of two days between sisters. One of the twins had more severe complaints, while the other one had milder. The more affected sibling had simultaneously started severe psychiatric symptoms with abrupt onset, including obsessions such as doubt, contamination/dirt, aggressive/catastrophic, superstitious/magical thoughts; compulsions such as washing, checking, and symmetry; anxiety symptoms such as free-floating anxiety, fear of the dark, somatic concerns and anxiety attacks with intermittent visual and/or auditory hallucinations; milder depressive symptoms such as anhedonia, anergia, avolition, ruminative thoughts, irritability, depressed mood and agitation; and sleep disturbances such as difficulty in falling asleep, interruptions of sleep, and/or nightmares. She also presented with attention-deficit, decreased aca-

ademic performance, irregular handwriting, and milder neurologic manifestations such as tremors in the hands, weakness of proximal muscles, intermittent complaints of tinnitus, dizziness, widespread headache, and/or joint pain. However, the less affected sibling exhibited only milder contamination obsession, cleaning compulsion, anxiety, attention deficit, fatigue; and milder neurologic complaints such as weakness, dizziness, and headaches.

The restrictive food intake and weight loss in both sisters were so worrisome that, both of them have consumed merely a few types of packaged and odorless food for months. When questioned in detail, both sisters have never had a concern about weight gain or struggling for weight loss, a special diet, or excess exercise, and the anamnesis regarding lack of an eating disorder was also verified by parents' reports. Prior hospital application was particularly done for investigating the etiology of somatic complaints, however, either restrictive food intake/weight loss or weakness/dizziness was not found to be associated with a gastroenterological, infectious, or any other medical condition. Any possibly suspected physical causes were also eliminated by the laboratory tests performed at first application to the pediatric clinic in the acute period of complaints, the sole positive result was mildly elevating plasma lymphocytes in both sisters (3320/ μ L and 2640/ μ L; normal reference ranges: 0.4-2.5/ μ L), and deficiency of vitamin-D in the more affected one of twin (9.19 ng/mL, normal reference ranges: 20-85 ng/mL); and the throat culture results of both were negative for GAS, while the PCR test of SARS-CoV-2 was also detected as negative for both of them (on February 2021). Since all these complaints, particularly being focused on restrictive food intake, weight loss, and fatigue, couldn't have been explained by an infectious or any other medical condition in acute stages, they had been immediately referred to psychiatric assessment with a strong suspicion of a severe eating disorder by pediatricians.

There had been no psychiatric application in the past premorbid history of both. No movement disorders or neuropsychiatric disturbances were previously reported in their medical history nor their family. However, they notably reported a history of a 15-day indoor quarantine period for whole family members, after the hospitalization of their grandmother (who have been living in their home) with a diagnosis of COVID-19-associated pneumonia. The symptoms of severe restrictive food intake, accompanied by simultaneous neuropsychiatric complaints abruptly started after two weeks of indoor quarantine in which twin sisters had been reported as asymptomatic for common respiratory or physical complaints of COVID-19.

In the premorbid history of these acute neuropsychiatric symptoms, both sisters have never had a recognized psychiatric symptom or a medical disorder. Moreover, a normal scholar and social functionality were described for both of them. This dizygotic twin's natal history consisted of prematurity (35 weeks of birth, with birth weights of 2300 and 2550 gr, and normal spontaneous vaginal delivery), yet they didn't experience any complications related to prematurity. Additionally, any significant individual or hereditary psychiatric condition which could be either at the diagnostic level or the subclinical symptom level was not detected according to parents' self-reports.

3. Results of laboratory tests and psychometric assessments

After a detailed psychiatric and physical examination, psychometric assessments, laboratory tests, and treatments through suspicion of PANS/PANDAS were planned and consultation with the pediatric neurology department was performed. The plasma autoimmunity panels such as *anti-TPO*, *anti-thyroglobulin*, *anti-endomysium*, *Anti-ds DNA*, *anti-DNAse*, and *Antistreptolysin-O* (three measurements in different times; ASO) were all in normal ranges (negative). The autoimmune encephalitis panel was negative. The plasma hormonal tests concerning thyroid functions (TSH, fT_4 , and fT_3), plasma vitamin and mineral levels, general urine analysis, positive and negative acute-phase reactants of infection such as sedimentation, C-reactive protein (CRP), or ferritin, were all detected in normal ranges. Plasma ceruloplasmin (0.18 g/L for both, nor-

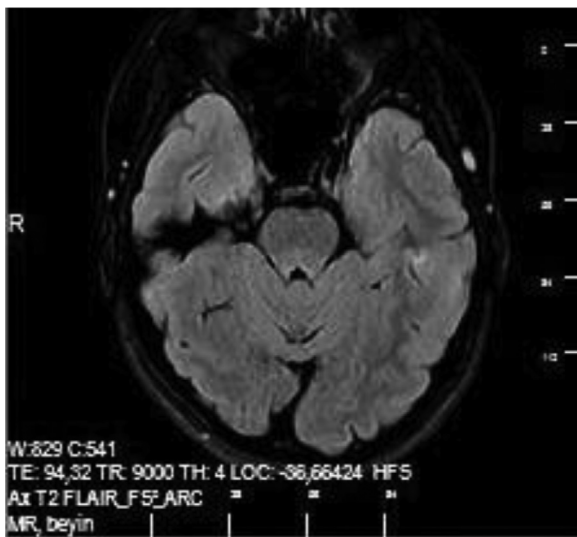


Fig. 1. Cranial MRI Illustration of Atrophic Vermian Folia in Cerebellum

mal reference ranges: 0.2-0.6) and copper (53.01 $\mu\text{g/L}$ and 51.33 $\mu\text{g/L}$, normal reference ranges: 2-80) were also normal.

The repeated throat cultures for both sisters were found as negative for GAS, and the results of PCR for SARS-CoV-2, repeating in the psychiatric application again, were negative. However, the plasma IgG of SARS-CoV-2 was notably positive ($> 10 \text{ mg/dL}$). The plasma serological study for main infectious agents (IgM levels) (Cytomegalovirus, Epstein-Barr virus, Hepatitis-A, -B, -C and -E virus, Herpes Simplex virus -1 and -2, Mycoplasma pneumonia, Toxoplasma gondii, Rubella virus, HIV, etc.) were all negative/normal. The notable findings of the psychometric assessments of more affected siblings and less affected siblings were as follows: Childhood Depression Scales (cut-off: 19) were 27 and 12; State / Trait Anxiety Inventory-Children Version were 61 / 55 and 54 / 47; Children's Yale-Brown Obsessive-Compulsive Scale - Total scores were 36 and 18; and, and total scores for Disgust Scale-Revised Form were 67 and 68. In neurological evaluation, *mild atrophy in vermian folia in cerebellum* (Fig. 1) and *'primary generalized active slow-spike wave (1.5-2 Hz) discharges (0.2-0.5 second, 10 times per monitoring)*' were detected in cranial-MRI and EEG of the more affected sibling. The results of MRI-diffusion and MRI-SWAN were all normal.

As the first treatment option in suspicion of PANS, proper psychotropic treatments and antibiotic agents (amoxicillin-clavulanate, 2 gr/day, for 21 days) were administered to both sisters. The more affected sibling was treated with fluoxetine (40 mg/day), risperidone (1 mg/day), and sodium valproate (20 mg/kg/day) while the less affected sibling with milder symptoms was treated with sertraline (50 mg/day). After one month following these treatment options, IVIG transfusion was required, because of mildly decreased, however, severely continuing psychiatric and somatic complaints. Surprisingly, the somatic complaints, restrictive food intake, OCD symptoms, severe anxiety with hallucinations, depression, and even mild neurologic symptoms were significantly decreased 1 week after the IVIG transfusion; and the patients had weight gain.

4. Discussion

PANS is a syndrome characterized by a broad clinical spectrum of neuropsychiatric comorbidities with an eating disorder, potentially triggered by infections by a variety of microorganisms (Swedo et al. 2012; Toufexis et al. 2015). Some common viral infections are known to directly infect the CNS or indirectly affect CNS by autoimmune and/or

cytokine-associated mechanisms, causing neuropsychiatric syndromes including cognitive, affective, behavioral, and perceptual impairments (Arciniegas and Anderson 2004). Until today, several bacterial and/or viral agent has been defined as etiological factor of PANS. However, to the best of our knowledge, there is no study, or even a case report concerning SARS-CoV-2/COVID-19-associated PANS.

To date, approximately 2-5% of cases of COVID-19 involve children, who appear to be less severely affected than adults, mainly with pulmonary symptoms. These age-dependent differences in disease expression and severity in pediatric population have clear implications for healthcare professionals. Children remain at high risk for incurring and spreading the virus, but majority of them remain asymptomatic. However, scarce data regarding acute and/or chronic neuropsychiatric results of SARS-CoV-2-associated infection in the pediatric populations have been harvested. A recent study concerning the psychosocial burden of the pandemic on children indicated psychological repercussions which were associated with prolonged quarantine, infection-anxiety, pervasive feelings of frustration and boredom, the disruption of formal education and contact with classmates/teachers, the lack of space at home, and loss/fear of loss of loved ones (Wang et al. 2020). Although there are many ways in which mental health might be adversely affected by a pandemic, psychiatric consequences of COVID-19 have been reported as little yet. However, clinicians must be alert both to strongly anticipated psychiatric results such as depression, anxiety, fatigue, or PTSB, and on rarely expected ones such as scarce neuropsychiatric syndromes (PANS, CANS, etc.) in the aftermath. Given the abrupt, complex, simultaneous onset and severe course of symptoms and fine response to immunomodulatory treatment (IVIG), the neuropsychiatric frame of our cases differs from the expected natural psychological consequences arising from the psychosocial burden of the pandemic on adolescents.

The ACE-2 receptor that is targeted for SARS-CoV-2 is expressed in the olfactory lining as well, and olfactory dysfunction has even been considered a biomarker for COVID-19. Moreover, 12-32% of cases with COVID-19 were reported as presenting with olfactory and gustatory disturbances (Lechien et al. 2020). So, the sudden and dramatic restrictive food intake, which was the starting and predominant symptom of these twin cases, might be also relevant to their olfactory and gustatory disturbances from COVID-19 even though all these symptoms have given response to psychotropic, anti-microbial treatments, and IVIG.

PANS research consortium suggests three complementary modes of intervention for PANS in newly published guidelines: 1. Treatment of symptoms with standard psychiatric care, behavioral, and supportive interventions, 2. Removal of the source of inflammation with antimicrobial treatments, 3. Administration of anti-inflammatory and/or immunomodulatory therapies (corticosteroids and/or intravenous immunoglobulin-IVIG) against immune disturbances (Cooperstock et al. 2017). Moreover, an initial course of antimicrobial treatment through streptococcal infection is strongly recommended in newly diagnosed patients with PANS, regardless of whether the identification of GAS infection or not (Cooperstock et al. 2017); and IVIG is established to be effective in case of exacerbations and recurrences (Kovacevic et al. 2015).

5. Conclusion and Perspectives

As the clinical spectrum of pediatric presentation of COVID-19 has yet to be established, clinicians should be aware of the potential for COVID-19 to present with other organ involvement, such as neuropsychiatric symptoms; and also of the possibility of depression, anxiety, fatigue, post-traumatic stress disorder, and scarce neuropsychiatric syndromes in the longer term. As seen in this case, when a child presents with other potential causes for neuropsychiatric symptoms also consisting of PANS, clinicians should consider SARS-CoV-2 as a potential agent, even in asymptomatic patients or with mild respiratory symptoms.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. None of the authors have any conflicts of interest or financial ties to disclose

Source of Funding

This study did not receive any specific grant from the public, commercial, or not-for-profit funding agencies.

Acknowledgments

Thank the departments of microbiology and infectious diseases of Dr. Sami Ulus Maternity, Children's Health and Diseases Training and Research Hospital.

References

- Allen, Albert-J, Leonard, Henrietta-L, Swedo, Susan-E, 1995. Case study: a new infection-triggered, autoimmune subtype of pediatric OCD and Tourette's syndrome'. *J Am. Acad. Child Adolesc. Psychiatry* 34 (3), 307–311.
- Arciniegas, David B, Anderson, C Alan, 2004. Viral encephalitis: neuropsychiatric and neurobehavioral aspects. *Curr. Psychiatry Rep.* 6 (5), 372–379.
- Chang, Kiki, et al., 2015. Clinical evaluation of youth with pediatric acute-onset neuropsychiatric syndrome (PANS): recommendations from the 2013 PANS Consensus Conference. *J. Child Adolesc. Psychopharmacol.* 25 (1), 3–13.
- Clapp, Megan, et al., 2017. Gut microbiota's effect on mental health: the gut-brain axis. *Clinics Practice* 7 (4), 131–136.
- Cooperstock, Michael S, et al., 2017. Clinical management of pediatric acute-onset neuropsychiatric syndrome: part III—treatment and prevention of infections'. *J. Child Adolesc. Psychopharmacol.* 27 (7), 594–606.
- Hesselmark, Eva, Bejerot, Susanne, 2019. Patient satisfaction and treatments offered to Swedish patients with suspected pediatric acute-onset neuropsychiatric syndrome and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *J. Child Adolesc. Psychopharmacol.* 29 (8), 634–641.
- Hoekstra, Pieter J, et al., 2005. Association of common cold with exacerbations in pediatric but not adult patients with Tic disorder: a prospective longitudinal study. *J. Child Adolesc. Psychopharmacol.* 15 (2), 285–292.
- Kovacevic, Miro, Grant, Paul, Swedo, Susan E, 2015. Use of intravenous immunoglobulin in the treatment of twelve youths with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *J. Child Adolesc. Psychopharmacol.* 25 (1), 65–69.
- Lechien, Jerome R., et al., 2020. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur. Arch. Otorhinolaryngol.* 277 (8), 2251–2261.
- Mao, Ling, et al., 2020. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* 77 (6), 683–690.
- Molina, Vered, Shoenfeld, Yehuda, 2005. Infection, vaccines and other environmental triggers of autoimmunity. *Autoimmunity* 38 (3), 235–245.
- Murphy, Marie-Lynd, Pichichero, Michael-E, 2002. Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS). *Arch. Pediatr. Adolesc. Med.* 156 (4), 356–361.
- Susan, E., Swedo, M.D., et al., 1998. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am. J. Psychiatry* 155 (2), 264–271.
- Swedo, SE, Leckman, JF, Rose, NR, 2012. Modifying the PANDAS criteria to describe PANS (pediatric acute-onset neuropsychiatric syndrome). *Pediatr. Ther.* 2 (2), 1–8.
- Thienemann, Margo, et al., 2017. Clinical management of pediatric acute-onset neuropsychiatric syndrome: part I—psychiatric and behavioral interventions'. *J. Child Adolesc. Psychopharmacol.* 27 (7), 566–573.
- Toufexis, Megan D, et al., 2015. Disordered eating and food restrictions in children with PANDAS/PANS. *J. Child Adolesc. Psychopharmacol.* 25 (1), 48–56.
- Troyer, Emily-A., Kohn, Jordan-N., Hong, Suzi, 2020. Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19, Neuropsychiatric symptoms and potential immunologic mechanisms. *Brain Behav. Immun.* 87, 34–39.
- Wang, Guanghai, et al., 2020. Mitigate the effects of home confinement on children during the COVID-19 outbreak. *Lancet North Am. Ed.* 395 (10228), 945–947.
- Wilbur, Colin, et al., 2018. PANDAS/PANS in childhood: controversies and evidence. *Paediatrics Child Health* 24 (2), 85–91.
- World Health Organization, WHO (2020), Mental health and psychosocial considerations during the COVID-19 outbreak, 18 March 2020, (World Health Organization).
- Zibordi, Federica, et al., 2018. CANS: childhood acute neuropsychiatric syndromes. *Eur. J. Paediatr. Neurol.* 22 (2), 316–320.