



Treatment Insights from Long COVID Syndrome Emerging as Neuropsychiatric Exacerbations in Autism Spectrum Disorder

Neda Banaei¹, Mahnaz Saremi^{2*}, Mona Akbari-Ahmadabadi³

¹Department of Biology, Faculty of Basic Sciences, Islamic Azad University of North Tehran, Tehran, Iran.

²Reference Health Laboratory, Ministry of Health and Medical Education.

³Department of Biology, Faculty of Basic Sciences, East Tehran Branch, Islamic Azad University, Tehran, Iran.

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*Corresponding author: Mahnaz Saremi, Reference Health Laboratory, Ministry of Health and Medical Education, Email: MahnazSaremi@gmail.com

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Abstract:

Even if the symptoms during the acute phase are minimal, COVID-19 not only results in severe respiratory problems but also long-term consequences. Significant long-term consequences are now being identified as neurological and neuropsychiatric problems. The onset of neuropsychiatric symptoms brought on by a lengthy COVID might be challenging to detect and treat in patients with behavioral problems, such as those with autism spectrum disorders (ASD). In this article, we describe three instances of ASD that showed a substantial worsening of neuropsychiatric symptoms after exposure to COVID-19 and subsequent difficulties controlling the post-COVID neuropsychiatric symptoms. The therapy intended to target COVID-19-induced immune reaction was delayed because Case 1 caught SARS-CoV-2 in the early phases of the epidemic. Case 2 had a verified COVID-19 exposure but showed no symptoms during the acute phase, however, she later had severe neuropsychiatric symptoms. Case 3 had a challenging course, in part because of underlying immunological dysregulation and the past use of many immunomodulating drugs. Significant variations in peripheral blood monocytes' generation of inflammatory and counter-regulatory cytokines were seen in cases 1 and 3, for which serial blood samples were taken. The instances discussed here show how COVID-19 has a significant impact on neuropsychiatric symptoms in ASD patients as well as how challenging it is to treat long-term COVID side effects.

INTRODUCTION

Our healthcare system was severely disrupted by the severe acute respiratory disorder coronavirus 2 (SARS-CoV-2)-which caused the coronavirus disease 2019 (COVID-19) epidemic. Both children and people with intellectual disabilities were affected, as was obvious (1, 2). It was shown that COVID-19 patients frequently experienced a long-term sequela that affected several organ systems, termed the "long COVID syndrome," as the pandemic expanded (3, 4). Both children and young people are impacted by this illness. Due in part to the absence of a precise case definition, the frequency of protracted COVID disorder in children is not yet fully characterized (5, 6).

A typical symptom of protracted COVID disorder is the cognitive disturbance, sometimes known as "brain fog," which is recorded in one out of every four to five post-COVID-19 individuals (7). Along with other neuropsychiatric symptoms such as anxiety, restless

sleep, exhaustion, and melancholy mood, this disease is characterized by deficits in attention, concentration, memory, speed of information processing, and executive function (7, 8). Such persistent post-COVID-19 neuropsychiatric symptoms may have a major negative impact on quality of life (QOL) and academic and occupational performance.

Long-term COVID syndrome patients often exhibit cognitive deficits that are similar to the disorder of cancer therapy-related cognitive impairment (CRCI), which is commonly recognized as a side effect of intrathecal methotrexate injection (9). Chronic fatigue syndrome (CFS) and CRCI have several characteristics (3, 10). Microglial cells have a role in the systemic inflammation brought on by modest levels of lipopolysaccharide (LPS) (9), which may result in reactive microglia in the white matter and monocyte/macrophage lineage cells being attracted to the brain (11,12).

It may be challenging to discern between the long-term effects of the above-mentioned neurological impairment in children and the psychological effects of the COVID-19 epidemic (5). COVID has enhanced parenting stress, which can lead to behavioral issues (13). This is especially true for parents of children with autism spectrum disorder (ASD), where it has been linked to increased levels of anxiety and depression as well as the development of more maladaptive behaviors in the child (14). It is even more challenging to discern between COVID-19-induced abnormal behavior and pre-existing neuropsychiatric problems if brain failure brought on by COVID-19 affects children who already have an intellectual handicap or other pre-existing neuropsychiatric illnesses, such as ASD.

ASD is a complicated developmental disability that is marked by poor social interaction, repetitive or restricting activities, and a high prevalence of coexisting diseases (15). It is anticipated that identification and treatment may be difficult for children with ASD who have brain damage as a long-term side effect of COVID-19. Such neuropsychiatric and neurological problems brought on by COVID-19 may be brushed off as typical ASD symptoms, losing the chance to treat COVID-19-induced neuro-inflammation and alleviate behavioral problems (16).

This article recounts three ASD individuals who had significant and long-lasting changes in their neuropsychiatric symptoms after taking COVID-19, changes that were difficult to treat. These instances highlight how challenging it is to treat the long-term neuropsychiatric effects of COVID-19 disease and the requirement for therapeutic approaches that specifically target COVID-19-induced immunological response.

MATERIALS AND METHODS

Research Topics

At Azad university organization, all individuals participated in the monocyte cytokine pattern evaluation methodology for ASD that was authorized by the institutional review board. Informed permission papers with parental signatures were acquired in every instance.

Profiles of monocyte cytokines

Monocytes from peripheral blood (PBMo) were extracted. PBMCs were separated using a Ficoll-Hypaque ultracentrifugation separation method. Using magnetic beads tagged with anti-CD3, CD7, CD16, CD123, and glycoporphin A, PBMo was further purified from PBMCs (monocyte MojoSort™ Isolation Kits, BioLegend's, MA, USA, Cat. No. 480019)

PBMo were grown overnight at a frequency of 5×10^5 /mL with or without innate immune system stimuli such as LPS, zymosan, CL097, and candida heat extraction as a source of β -glucan. PBMos were incubated for

24 hours in RPMI 1640 containing additives with LPS (0.1 μ g/mL, GIBCO-BRL, Gaithersburg, MD, USA), zymosan (50 μ g/mL, Sigma-Aldrich, USA), C097 (liquid derivative of imidazoquinoline, 20 μ M, InvivoGen, USA), and candida heat extract HCKA, heat killed candida albicans (107 cells/mL, InVivogen, CA) as a source of β -glucan. the number of cytokines (IL-1 β , IL-6, IL-10, IL-23, TNF-, sTNFR2, IL-12p40, TGF- β , and CCL2) in the growth supernatant was determined by ELISA (eBiosciences, San Diego, California). ELISA protocol was performed according to manufacturer's instrument.

RESULTS

Presentation of a Case

Case 1

The first case was a 25-year-old boy with ASD who was monitored at an allergy/immunology center. He arrived with recently developed extreme weariness, broad muscle problems, and increasing fluctuation of behavioral symptoms associated with an autism spectrum disorder. This came after a minor respiratory illness that had happened one month before the Tehran COVID-19 lockdown began. He had previously received diagnoses for common variable immunodeficiency, multiple seizures from intractable epilepsy, and ASD (level III) (CVID). Immunomodulatory medications were used to manage his refractory seizures (sirolimus and anakinra). Supplemental immunoglobulin (Ig) administered during biweekly subcutaneous (SQ) infusion helped manage recurrent bacterial infections and bacterially-induced seizure complexes. Additionally, he was taking azithromycin three times per week as part of a prophylactic program. This was brought on by a history of widespread cholesteatoma exacerbated by severe mastoiditis, which necessitated numerous surgical resections. Around the same time, his mother began to have similar respiratory problems, severe exhaustion, and "brain fog." It was determined that this patient and his mother both had COVID-19 due to the presence of SARS-CoV-2 antibodies. After each immunological insult (usually a microbial infection), he had a history of escalating behavioral symptoms (irritability, mood swings, anger, self-harming activities, and disrupted sleep), and even cognitive decline. He was administered a variety of anti-inflammatory treatments (NSAIDs, oral steroid burst, etc.), as well as maintenance immunomodulating pharmaceuticals provided to control his seizures since it was believed that his illness was related to post-infectious neuroinflammation. He and his mother both proceeded to have chronic exhaustion, "brain fog," joint and muscular pain, and dysautonomia problems, which were not alleviated by the anti-inflammatory drugs to which he had previously reacted. He and

his mother were severely affected by these problems, which harmed their quality of life. Mycophenolate was tested, however, it only partially relieved symptoms. Colchicine (0.6 mg dose) was initiated to inhibit such signaling pathway activation as a result of a better knowledge of neuropsychiatric symptoms as a long-term sequela of COVID-19 and stimulation pathways via SARS-CoV-2. He and his mother both reacted well to colchicine, with a significant improvement in long-term COVID problems. Both his mother's and his symptoms improved six months after taking colchicine. According to his mother, he did not, however, fully revert to his prior baseline. We were able to identify his deteriorating neuropsychiatric problems as long-term COVID-19 sequelae in his instance because of the comparable symptoms that his mother had experienced.

Case 2

Case 2 came into the clinic for the first time at the age of 14 as a result of repeated illnesses. After a noticeable delay in progress led to the diagnosis of ASD at the age of 36 months, she began having seizures at the age of 40 months. These seizures began as partially complicated seizures but later turned into secondarily generalized seizures. Many antiepileptic medications were unable to stop her seizures (AEDs). Between the ages of 6 and 11, she saw positive results with a modified Atkin's diet and stopped having seizures. The onset of puberty did, however, cause a recurrence of clinical seizure complexes. Her neurologist had recommended a high dosage of valproate at the time of her first presentation (375 mg in the morning, 1,125 mg at lunchtime, and 2,250 mg at bedtime). By the time she was 12 years

old, she had developed a persistent respiratory illness. She was evaluated for secondary immunosuppression brought on by AED usage because valproate-induced hypogammaglobulinemia has been documented (18). Pneumococcal vaccination responses were diminished, according to our early workup (PPV23). Her recurring respiratory infections were under control, and the frequency of her seizures reduced thanks to further SQ Ig. After that, she and every member of the family caught COVID-19. Due to her complete COVID-19 vaccination before the COVID-19 exposure, the patient didn't exhibit any symptoms. Her valproate dosage was gradually tapered down beginning at the age of 15. Her mother didn't notice any significant acute symptoms; such as taste loss. The individual could verbally convey all of his or her symptoms. She had severe exhaustion, a lack of appetite, and weight loss (>20 lbs over 2 months from the beginning of neuropsychiatric symptoms) two to three weeks after developing COVID-19. She was prescribed celecoxib 100 mg bid for two weeks before switching to colchicine 0.6 mg bid since it was determined that she had been exposed to COVID-19 before the commencement of her neuropsychiatric symptoms. After using colchicine for three months, her neuropsychiatric problems progressively improved over 10 to 12 weeks, in part because of her gastrointestinal (GI) issues (mainly loose stool). After contracting COVID-19, she did not have any seizure clusters. Her neuropsychiatric problems significantly increased when colchicine was stopped, manifesting as extreme mood swings and tantrums that were managed by increasing the dosage of valproate. Celecoxib is still needed for her every



Fig 1. Changes in spontaneous generation of TNF- α , IL-1 β , IL-12, TGF- β , and IL-10 by purified peripheral blood monocytes in Cases 1 at different time point. time point 1: before COVID-19, time point 2: after suffering from COVID-19, and time point 3: after colchicine treatment.

two weeks to treat behavioral symptoms and flare-ups brought on by modest immunological shocks such as microbial infection. Her prior monocyte cytokine pattern suggested high responses to innate immunity simulating viral infection, which should be successfully counter-regulated by celecoxib, even though we did not study it after her SARS-CoV-2 exposures. Celecoxib worked well to reduce small flare-ups.

Case 3

Case 3 involves a boy patient with ASD who first visited our pediatric allergy/immunology department at the age of 6 with worries about changing maladaptive behaviors that were often brought on by immunological insults. He was given an ASD diagnosis when he was 3 years old, but the conventional ASD therapies have not worked for him. No symptom alleviation was offered by the hematopoietic stem cell transplant he had at the university a year before his first visit. He has since received high-dose intravenous immunoglobulin (IVIg) therapy for autoimmune encephalitis (AE). But thorough AE testing came up empty on any AE-related autoantibodies. Later, SQIg was substituted for IVIg to reduce post-infectious neuroinflammation. Several therapies were explored when he arrived at this facility, including several neurotropic medicines, antioxidants, and immunomodulating drugs (mycophenolate, mTOR inhibitor, etc.). A novel discovery of vEEG anomalies led to the selection of the mTOR inhibitor sirolimus (19). Following a transient symptomatic alleviation with sirolimus, the vEEG returned to normal. No harmful gene variations were found after extensive genetic testing, including whole exome and

genome sequencing (WES and WGS). An extensive immunological evaluation with an emphasis on neuroinflammation at another hospital produced no notable outcomes. At age 9, the vEEG changed once again due to the reappearance of clinically proven epileptic activity. The purpose of starting Anakinra was to limit seizure activity while providing transient symptom relief. However, it became very challenging to control his behavioral problems. Then, everyone in the family had COVID-19, and his behavioral problems became worse. Around that time, a vEEG showed generalized epileptic activity. Other healthcare professionals treated him for many months for seronegative AE with an oral steroid bolus (dexamethasone 12 mg/day 3 every month) without any symptomatic alleviation. Since his most recent deterioration of behavioral issues was probably brought on by COVID-19, baricitinib, a JAK1/2 inhibitor, was begun and helped to alleviate some symptoms. Due to increasing epileptic activity after ceasing sirolimus post-COVID-19, sirolimus was restarted. It had been stopped after acquiring COVID-19. With the help of baricitinib, sirolimus, and mycophenolate, his health stabilized, even though he continued to have flare-ups of neuropsychiatric symptoms after each immunological assault. A brief treatment of colchicine helped to normalize his behavioral problems due to a recent immunological assault. Then, for a brief period, minocycline was used in the hope that inhibiting indoleamine 2, 3-dioxygenase (IDO) function would provide further symptomatic relief for the acute worsening of his neuropsychiatric symptoms, which were ostensibly brought on by a viral illness. It did

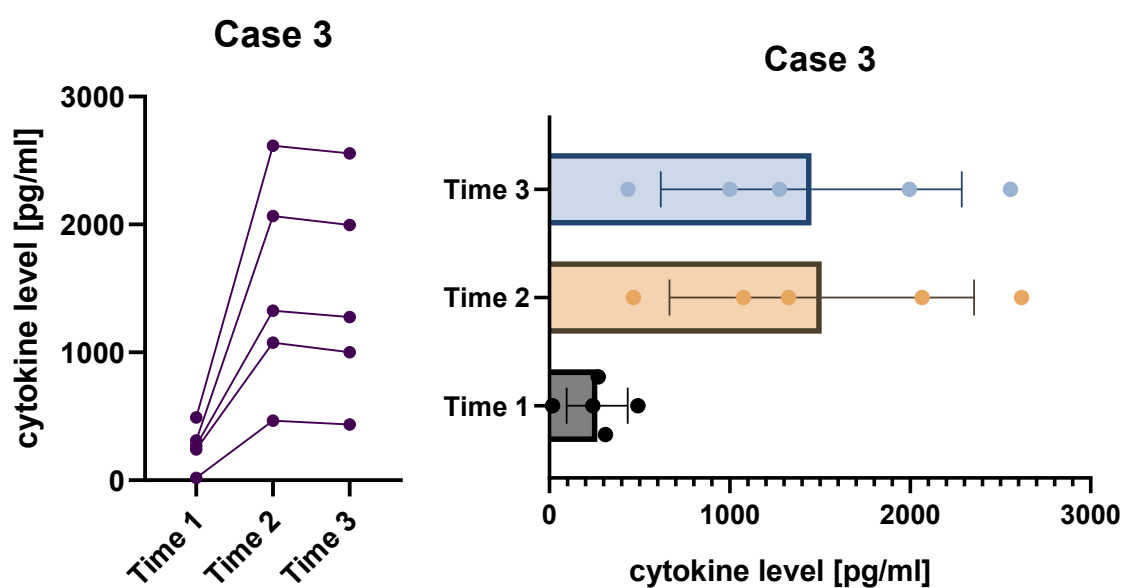


Fig 2. Changes in spontaneous generation of TNF- α , IL-1 β , IL-12, TGF- β , and IL-10 by purified peripheral blood monocytes in Cases 3 at different time point. time point 1: before immune activation, time point 2: after immune activation by viral infection (not SARS-CoV-2), time point 3: after suffering from COVID-19.

alleviate certain symptoms..

Monocyte Cytokine Profiling Variations Prior to and Following COVID-19

For Cases 1 and 3, it was possible to compare the monocyte cytokine patterns before and after being infected with SARS-CoV-2. In Case 1, the most striking observation was a rise in the spontaneous generation of inflammatory (IL-1 β), tumor necrosis factor- α (TNF- α), and IL-12) and counter-regulatory (IL-10 and TGF- β) cytokines 14 months after COVID-19 disease (time point 2). 4 months after commencing colchicine, these increases recovered to their baseline levels (time point 3). In Case 3, there was a considerable aggravation of his neuropsychiatric symptoms that increased the endogenous production of inflammatory cytokines (IL-1 β , IL-10, IL-12, and TGF- β) before COVID-19 treatment (time point 2). Eight months after being exposed to COVID-19, a similar rise in monocyte inflammatory cytokines was still present (time point 3). The TNF- α synthesis also rose spontaneously after COVID-19. For both Cases 1 and 3, it seems that COVID-19 had less of an impact on the generation of these mediators in reaction to innate immunity cues. Significant variations in IL-6 serum concentrations throughout the antepartum and postoperative phases have been linked to an increased risk of ASD, according to the research (20). In the situations that are being discussed, we have analyzed IL-6 generation but have not seen any notable alterations. The fact that plasma IL-6 concentrations reflect synthesis from numerous cellular origins, not only monocytes, and that they have a lengthy half-life in the serum may be related to this.

DISCUSSION

According to reports, the clinical presentation of protracted COVID illness often includes neurological and neuropsychiatric symptoms including “brain fog.” Even if one only has modest COVID-19 symptoms, this may still happen after getting over the acute period (21). In ASD participants for whom the early stages of COVID-19 were either moderate or asymptomatic, the examples described here demonstrate a range of clinical symptoms of long-term COVID-19 aftereffects. According to certain theories (21, 22), a percentage of people with ASD may have neuroinflammation that is brought on by intricate interplay between hereditary and environmental variables. Such ASD patients should have neuroinflammation flare-ups in response to an immunological stimulation that activates the systemic immune system; this condition is likely to happen in conjunction with a viral disease. Due to a strong and persistent immunological activation, the formation of COVID-19 and its long-term repercussions have been found to impact various organ subsystems, such as the brain (23–25). Therefore, COVID-19 is

anticipated to have a significant impact on the level of neuroinflammation in ASD patients who already have an inflammatory component. However, when the COVID-19 epidemic first started, this wasn't first understood. In our experience, several ASD patients had thorough examinations for ailments like AE and other autoimmune diseases that have symptoms of ASD. Case 1 had an autoimmune examination because of his ongoing lethargy and musculoskeletal problems. The fact that his mother had identical clinical symptoms after getting COVID-19 at about the same period as the patient in his instance, however, gives us a hint for identifying the severe, long-lasting consequences of COVID-19. We were able to identify the ongoing *in vivo* activation of monocytes and macrophages thanks to the rise in spontaneous monocyte inflammatory cytokines (Figure 1) as well. We weren't yet sure which immunomodulating drugs would be effective in managing his condition. Others' research on the immunological activation caused by COVID-19, however, highlighted the significance of the signaling pathways that activate type I IFNs, which then activate the inflammasome systems (23, 24, 26). These results prompted us to think of using inflammasome blockers to modulate the downregulation stimulation of cells of the monocyte/macrophage lineage. A study with inhibitors of generated phagocytic cells was deemed reasonable given that this individual has been receiving treatment with an mTOR blocker (sirolimus), despite reports of the continued presence of stimulated T and B cells (26). Additionally, colchicine has been shown to have a positive effect on COVID-19, however, most of these publications only addressed the acute phase of the disease (27–29). Even one year after COVID-19, we saw a rise in the spontaneous generation of monocyte cytokines, which led us to believe that colchicine should be tested. He did show positive reactions. The significance of carefully choosing immunomodulating drugs appropriate for each condition may be highlighted by this example.

Despite the patient in Case 2 being asymptomatic and in the acute period of COVID-19, we were able to identify the likelihood of protracted COVID-19 immediately. Given her subsequent hypogammaglobulinemia, which was probably brought on by the high dosage of valproate (17), and Case 1's positive clinical outcomes with colchicine, she also was given colchicine and had a positive clinical outcome. However, this participant's neuropsychiatric issues became worse after the colchicine was stopped because of GI difficulties. This example also demonstrates the potential for even asymptomatic COVID-19 to potentially have serious neurological consequences, necessitating the potential need for an extended course of immunomodulating medications that target protracted COVID. Among the most challenging examples, we came

across was Case 3, which is depicted in this article. Despite a trial of many immunomodulating drugs, the patient's immune system was in this instance already noticeably active *in vivo*, as seen in Figure 1. He most likely had neuroinflammation that was made worse by COVID-19. After he developed COVID-19, we used baricitinib, a JAK1/2 inhibitor, to disrupt downstream type 1 IFN signal transduction given the past usage of other immunomodulating drugs that targeted different signaling pathways. In extreme COVID-19 patients, baricitinib has been shown to have positive immunomodulating actions and has been suggested as a viable COVID-19 treatment drug (30, 31). Baricitinib produced some clinical results in the patient, but once the immune system was subsequently activated by infected contacts (not COVID-19), its pharmacological effects vanished (32-34). To suppress the post-COVID-19 immune reaction, colchicine was subsequently administered to have a wider anti-inflammatory impact. The patient appeared to gain from receiving therapy that included both colchicine and baricitinib. This serves as an example of a situation in which a combination of several immunomodulating drugs may be necessary (30, 35). In example 1, the individual was already receiving mTOR inhibitor therapy (sirolimus). The good response to colchicine that was seen may have benefited from this. Based on these three clinical studies, it is challenging to provide comprehensive management recommendations for extended COVID in ASD patients because of the well-known variability of ASD. Instead, the instances are offered to highlight the difficulties in treating ASD patients and the potentially severe consequences of COVID-19 on these individuals. The instances mentioned may point to the necessity for individuals with ASD to have customized care, particularly if immune-mediated inflammation contributes to their behavioral dysfunction, as it does in extended COVID-19 disorder.

CONCLUSION

Overall, the three instances show that, even though COVID-19's clinical signs are moderate or asymptomatic, the virus may have dramatic, long-lasting effects on immunological activation, which might manifest as a marked worsening of neuropsychiatric symptoms in ASD participants. Such late-onset, long-lasting impacts of COVID-19 may be readily disregarded in the ASD community due to pre-existing, challenging-to-treat ASD behaviors and inadequate expressive language. Treatment of ASD individuals with extended COVID disorder will need a deeper understanding of the condition and available therapy alternatives.

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