

Abulia major and hypoactive delirium in COVID-19 reversed with methylprednisolone pulse therapy

Luiz Gonzaga Francisco de Assis Barros D'Elia Zanella (✉ luiz.zanella@hc.fm.usp.br)

University Hospital of São Paulo University <https://orcid.org/0000-0002-3166-5633>

Luiz Gonzaga Francisco de Assis Barros D'Elia Zanella (✉ luiz.zanella@hc.fm.usp.br)

University Hospital of São Paulo University

Case Report

Keywords: Methylprednisolone pulse-therapy, COVID-19, Dementia

Posted Date: August 2nd, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1804738/v4>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abulia major and hypoactive delirium in COVID-19 reversed with methylprednisolone pulse therapy

LUIZ GONZAGA FRANCISCO DE ASSIS B D ZANELLA

Corresponding author: LUIZ GONZAGA FRANCISCO DE ASSIS B D ZANELLA, luiz.zanella@hc.fm.usp.br

Abstract

Background: Sars-CoV-2 is a member of the genus Betacoronavirus like the two other coronaviruses viz. SARS-CoV (severe acute respiratory syndrome coronavirus) and MERS-CoV (Middle East respiratory syndrome coronavirus). SARS-CoV-2 infection has been associated with neuropsychiatric manifestations in acute and chronic COVID-19 (long COVID-19 syndrome), resulting in social consequences and worsening people's quality of life. **Case description:** This article is a scenario of two cases of neurological manifestations resulting from infection by SARS-CoV-2 that were reversed with methylprednisolone in a pulse therapy regimen. The first case presents a young patient with symptoms similar to those existing in patients with Alzheimer's and Parkinson's diseases, whose final and presumable diagnosis was Abulia major. The second case exemplifies an elderly person admitted to the hospital due to hypoactive delirium triggered by a urinary tract infection hypothesis. The final diagnosis was hypoactive delirium secondary to COVID-19, with urinary manifestations from SARS-CoV-2 kidney injury. **Discussion/Conclusion:** The purpose of this article is to warn about phenomena related to COVID-19, whose treatment can be performed with high doses of corticosteroids and with drugs that act positively on dopaminergic and serotonergic pathways. Patient exams and more information are available in the Appendix of this article.

Keywords: case report, Methylprednisolone pulse-therapy, COVID-19 Dementia.

Introduction

COVID-19 is a new disease that causes systemic disease, with the lungs just one of the injured organs. Neuropsychiatric symptoms have been reported in both acute COVID-19 and chronic inflammation triggered by SARS-CoV-2 infection.

This article presents two case reports, whose neuropsychiatric phenomena appear to have a causal relationship with SARS-COV-2 infection, both treated with methylprednisolone with good evolution.

Timeline

2022-07-31	COVID-19 Symptoms (The dates are hypothetical in order to preserve the patient's identity, but respect
------------	---

the chronology of the interventions)	
2022-08-14	Dementia symptoms' onset
2022-08-17	Neurology's and Psychiatric's assesment, mood disorder drugs, worsenig of the symptoms
2022-10-22	Infectious Diseases specialist assessment and 10 days of follow up
2022-11-03	Methylprednisolone pulse-therapy and good evolution after 12 hours of the corticosteroid infusion.
2023-11-21	Onset of the symptoms, but with less magnitude shown one year ago. Methylprednisolone 1mg/kg/day and good evolution. (diagnose: Abulia minor, encephalitis and Abulia major one year ago)

Narrative

REPORTED CASES

Case 1:

A 40 - year - old man, married, presented rapidly and progressive dementia with signs and symptoms that resemble Alzheimer's and Parkinson's diseases: the patient lost the ability to find and perform common daily tasks progressively. He forgot the sequence of undressing to take a shower; he did not know how to use cutlery for his meals, having to be reminded by his wife how he should conduct tasks. Associated with this scenario, he had tremors of a Parkinsonian characteristic. For 2 months, neurologists and psychiatrists evaluated him and prescribed behavioural disorders drugs. Exams ordered by neurology: cranial computed tomography, cranial magnetic resonance with no significant changes, laboratory tests not worthy of note (appendix). Approximately 15 days after the currently symptoms the patient had been diagnosed with oligosymptomatic COVID-19, without hospitalization. His wife and children remained with negative serology even with flu-like symptoms during the same patient's symptomatic period. Called to evaluate the case: approximately 10 days of follow up was performed and requested more laboratorial assessments such as HIV serology, CMV viral load, EBV, and herpes virus and all exams were negative, except for IgG CMV being positive. Autoimmunity evidence is also negative (appendix).

During this period, patient's wife had information about hypotheses, and material about post-COVID-19 neurological manifestations was given to her, even COVID-19 being a new disease with shortage of material and publications about neuropsychiatric symptoms. After checking the exams already requested and following the patient's evolution for 10 days, some diagnostic possibilities were made: post-COVID-19 autoimmune encephalitis or neuropsychiatric manifestations caused by toxic kynurenine byproducts. Both have treatments based on high doses of corticosteroids.

In view of the situation without improvement after 2 months, given the exams and after the introduction of these new hypotheses, we jointly opted to perform methylprednisolone pulse for 3

days with the possibility of performing immunoglobulin in case of refractoriness, that is, a decision that respected the wife's understanding of the subject.

The protocol and patient's evolution are described bellow:

1. **First day (D1): METHYLPREDNISOLONE 1000 mg, intravenous, was performed, via infusion pump in 60 minutes.**
2. **Ivermectin 6 mg, two tablets as prophylaxis against disseminated strongyloidiasis.**
3. **Promethazine 25 mg, oral tablets, to prevent agitation, in addition to its anti-inflammatory effect on the central nervous system.**
4. **Citalopram 40 mg as an adjunct to treatment considering Serotonin and Dopamine deficiency after Sars-CoV-2 infection.**
5. **L-Dopa/Benserazide 100/25 mg, two oral tablets.**
6. **Vital signs were assessed, and no significant changes were noted.**

Evolution: patient evolves after 8 hours of drug infusion with normalization of cognitive function in a surprising way. During the first three days, he presented periods of neurological fluctuation, usually associated with a physical or psychological stressor. The prescription of rest for 1 month was followed. The patient had a good evolution, with no return to dementia.

He was under therapy with 1000 mg of methylprednisolone for two more days with a progressive decrease in the following regimen:

Prednisolone 80 mg for 3 days, 60 mg for 3 days, 20 mg for 3 days, and 10 mg for 3 days. Repeating 10 mg in 7 days, and after 14 days.

The phenomena presented by the patient resembled a mixture of Parkinson's disease (PD) and Alzheimer's disease (AD), similar to rapidly and progressive dementia. Having performed tests that could be requested and associated with the patient's clinical manifestations, the diagnosis was not closed, but there were two main possible hypotheses: a) anatomical: central nervous system; syndromic: dementia-like manifestations of AD and PD; etiologic: a) possibly by toxic kynurenine by-products by IDO-1-mediated inflammation, depletion of dopaminergic and serotonergic pathways by ACE-2 internalization by SARS-CoV-2, or b) formation of autoantibodies, but with negative serology resulting from SARS-CoV-2 infection.

After 1 year of the manifestations and the resolution of the condition, the patient had a new infection by SARS-CoV-2 (with positive RT-PCR for SARS-CoV-2); however, milder than the first. A few days after the onset of symptoms, the patient began to experience tremors, anhedonia, and loss of self-confidence, requiring confirmation from the wife to perform any type of actions or even to answer any questions that were asked. He also showed an attitude of muteness,

increasingly silent and not very reactive to situations. Initially, I called the patient by telephone, where he showed himself with spontaneous speech, reporting the changes he had realized in himself: unwillingness to perform daily activities, sadness, loss of self-confidence, and motor slowing. In a second moment, via videoconference, the patient was silent, and for each question made by me, he needed confirmation from his wife. Unintentionally, this situation sets up "Miller Fisher's telephone effect" (appendix),

The possible diagnoses were, in the first COVID-19, *Abulia major* and, in the second, *Abulia minor*. For this new situation, the use of prednisolone 1 mg/kg/day for 3 days, L-dopa and citalopram triggered a global improvement in the patient. A joint discussion was performed with a psychiatrist who was performing the follow-up of the case.

Case 2:

Man, 93 years old, married, independent of performing daily activities, myelodysplasia as a comorbidity [Katz =5 and Lawton = Partially dependent for 5 activities (Appendix)], is admitted to the emergency room due to acute hypoactive delirium. Infection screening was performed. He had a chest X-ray without evidence of pneumonia, a blood count with mild anaemia associated with myelodysplasia, leukocytes ~25,000 (slightly more than the patient usually presents in normal situations due to his comorbidity), and urine routine: leukocyturia 70,000 haematuria: 10,000, hyaline casts). The patient was initially diagnosed with delirium secondary to urinary tract infection. However, when chest tomography was requested, it showed the tomographic pattern of acute COVID-19 (Appendix). The patient began to present sluggishness 4 days ago, so it was assumed that the patient had been symptomatic for approximately 5 days, consistent with the chest tomography image presented (Appendix).

According to epidemiology, signs and symptoms, laboratory changes and tomographic imaging, COVID-19 was the main diagnosis. Urinary alterations are compatible with the lesions caused by SARS-CoV-2 in the renal parenchyma, which have often been confused with urinary tract infections. The patient's daughter signs a consent form, and a pulse therapy regimen was performed with Methylprednisolone 250 mg once a day for three days¹. The patient evolved to have an improved condition. He did not develop cytokine storm syndrome and was discharged on the fifth day of hospitalization.

Discussion

SARS-CoV-2 is a different virus, as it does not even follow the pattern of antibody production as it is used to see in most infectious diseases and this fact makes the diagnosis unlikely if physicians do not consider the patient's clinical and radiological image. Mental confusion, mood changes, difficulty in sedation, fatigue and chronic pain are associated with neuropsychiatric manifestations of COVID-19²⁰. There are still plenty of doubts about the probable causes, but the

pathophysiological explanation can be given by some hypotheses: a) kynurenine toxic products and tryptophan deficiency due to the internalization of ACE-2 in the intestine; b) adenosine pathway; c) development of autoimmune meningoencephalitis; d) lymphopenia and immunosuppression (appendix).

Despite more controversies that exist about the use of methylprednisolone and corticosteroids in general, it has been the solution for COVID-19. When used properly and at the right time, the progression of the disease can be blocked.

Patient Perspective

The two cases presented are in acute situations in patients who were previously healthy and independent or partially dependent to perform daily activities. We are facing a new virus with singularities that are still obstacles that prevent the realization of adequate therapy. It is essential to highlight that medical action must always be based on the ethics that govern the medical profession, on not harming, on offering comfort when there is no possibility of cure—always judging each situation properly and considering that the patient has a family that needs support. The use of corticosteroids, although controversial, has gained increasing evidence in the treatment of COVID-19, with benefits when used on time and in high doses. Corticosteroids are historically used to treat viral or autoimmune meningoencephalitis and the cases presented are examples of good use of the drug, promoting patients' improvement of symptoms with a return to the health status they had before they became ill.

All the families involved signed a consent form for the data to be published; in addition, both families provided me with all the exams to help with the publication of the reported cases. Methylprednisolone doses were based on the study published by Maryan Edalatfard et al. In addition, the higher doses between 500 and 1000 mg of Methylprednisolone were based on other publications on the subject and on the preliminary results of the COVER-ME-UP study, based on the Tehran protocol. The COVER-ME-UP study was carried out after approval by the National Research Ethics Committee (Brazil) (CONEP: 39196620.2.0000.5463; Authorization number: 4.341.587) and after approval by the ethics committee of the Hospital where the study was carried out.

Conclusion

Corticosteroids have side effects, but they are medicines that have been used for many years, and in the face of an inflammatory disease due to SARS-COV-2 infection, the nonspecific target of steroids has been our best treatment¹⁰

Acknowledgements

I dedicate this work to all COVID-19 patients who have died or who remain with sequelae.

To my colleagues in the Emergency Room of the University Hospital of the University of São Paulo.

To the patients' families that had the reported cases in this article.

References

1. Edalatifard M, Akhtari M, Salehi M, et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. *European Respiratory Journal* [Internet] 2020;56(6):2002808. Available from: [/pmc/articles/PMC7758541/?report=abstract](#)
2. Zanella LGF de ABD. NEUROCOV/PSYCCOV: Neuropsychiatric Phenomena in COVID-19 - Exposing Their Hidden Essence and Warning against Iatrogenesis. *Journal of Infectious Diseases and Epidemiology* [Internet] 2021 [cited 2021 Aug 27];7(8):222. Available from: <https://www.clinmedjournals.org/articles/jide/journal-of-infectious-diseases-and-epidemiology-jide-7-222.php?jid=jide>
3. Barros D'Elia Zanella, L.G.F.A.; de Lima Galvão L. The COVID-19 Burden or Tryptophan syndrome: autoimmunity, immunoparalysis and tolerance in a tumorigenic environment.
4. Kamal YM, Abdelmajid Y, Madani AAR al. Case report: Cerebrospinal fluid confirmed COVID-19-associated encephalitis treated successfully. *BMJ Case Reports* [Internet] 2020 [cited 2021 Sep 8];13(9):237378. Available from: [/pmc/articles/PMC7497137/](#)
5. Mor A, Tankiewicz-Kwedlo A, Krupa A, Pawlak D. Role of Kynurenine Pathway in Oxidative Stress during Neurodegenerative Disorders. *Cells* 2021, Vol 10, Page 1603 [Internet] 2021 [cited 2021 Oct 9];10(7):1603. Available from: <https://www.mdpi.com/2073-4409/10/7/1603/htm>
6. Kulisevsky J, Poyurovsky M. Adenosine A2A-Receptor Antagonism and Pathophysiology of Parkinson's Disease and Drug-Induced Movement Disorders. *European Neurology* [Internet] 2012 [cited 2021 Aug 15];67(1):4–11. Available from: <https://www.karger.com/Article/FullText/331768>
7. Attademo L, Bernardini F. Are dopamine and serotonin involved in COVID-19 pathophysiology? [Internet]. *European Journal of Psychiatry*. 2021 [cited 2021 May 29];35(1):62–3. Available from: [/pmc/articles/PMC7598536/](#)
8. Zanella LGF de ABD, Paraskevopoulos DK de S, Galvã L de L, et al. Methylprednisolone Pulse Therapy in COVID-19 as the First Choice for Public Health: When Right Timing Breaks Controversies—Emergency Guide. *Open Journal of Emergency Medicine* [Internet] 2021 [cited 2021 Aug 27];9(3):84–114. Available from: <http://www.scirp.org/journal/PaperInformation.aspx?PaperID=111400>

Author Affiliations

1. LUIZ GONZAGA FRANCISCO DE ASSIS B D ZANELLA, luiz.zanella@hc.fm.usp.br

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [finALAPPENDIX.docx](#)