RESEARCH ARTICLE

Remitting neuropsychiatric symptoms in COVID-19 patients: Viral cause or drug effect?

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Abstract

Numerous reports of neuropsychiatric symptoms highlighted the pathologic potential of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its relationship the onset and/or exacerbation of mental disease. However, coronavirus disease 2019 (COVID-19) treatments, themselves, must be considered as potential catalysts for new-onset neuropsychiatric symptoms in COVID-19 patients. To date, immediate and long-term neuropsychiatric complications following SARS-CoV-2 infection are currently unknown. Here we report on five patients with SARS-CoV-2 infection with possible associated neuropsychiatric involvement, following them clinically until resolution of their symptoms. We will also discuss the contributory roles of chloroquine and dexamethasone in these neuropsychiatric presentations.

KEYWORDS
chloroquine, corticosteroids, COVID-19, neuropsychiatric, SARS-CoV-2

1 | INTRODUCTION

Novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogen responsible for the coronavirus disease 2019 (COVID-19) pandemic, a disease that primarily affects the respiratory tract, causing infectious pneumonia and respiratory failure in severe cases.[1] However, as the pandemic evolved, numerous reports of neuropsychiatric symptoms highlighted the pathologic potential of SARS-CoV-2 and its relationship with the onset and/or exacerbation of mental disease.[2,3]

Here we report on five patients with SARS-CoV-2 infection with possible associated neuropsychiatric involvement. We will also discuss the contributory roles of chloroquine (CQ), and dexamethasone (DX) to these neuropsychiatric presentations.

2 | CASE SERIES

2.1 | Case 1

In March 2020, a 58-year-old male pilot with no remarkable clinical history presented to the University Hospital of Caracas (UHC), Venezuela, with 6 days of fever (between 38.3 °C and 39 °C), headache, dry cough, and dysgeusia. Three weeks prior, he traveled to Spain, Dominican Republic, and Trinidad and Tobago before returning to Caracas. His wife reported that the family had noticed changes in the patient's behavior, including intermittent anxiety and logorrhea. At presentation (Day 0), the patient was fully alert, was auto- and allopsychic oriented, and had an unremarkable neurologic examination. A nasopharyngeal specimen was submitted to the Rafael Rangel National Hygiene Institute, where SARS-CoV-2 infection was confirmed using real-time reverse transcription polymerase chain reaction (rRT-PCR). The patient was managed supportively as an outpatient, and his fever and respiratory symptoms were self-limited and resolved at Day 5.

However, at Day 12, he returned to the hospital and presented with increased anxiety. He was afebrile (36.5 °C) and vital signs were stable. A repeat nasopharyngeal specimen was still positive for SARS-CoV-2, and he was admitted. He was treated with CQ 155 mg orally every 12 h for 7 days, plus enoxaparin 40 mg subcutaneously every 24 h for 10 days, per Venezuelan Ministry of Health guidelines.[4] During his hospital course, he remained afebrile, and his vital signs were stable. However, he demonstrated increased anxiety and spent multiple hours on his smartphone researching COVID-19 disease and believed he understood the detailed mechanisms of his infection; however, he was not evaluated by psychiatry during his course. He was discharged at Day 26 after two consecutive nasal swabs tested negative for SARS-CoV-2.

At Day 56, the patient was brought back to the hospital by his wife, who reported worsening psychiatric symptoms since the previous discharge. Specifically, he presented with insomnia, pressured rate of speech, and logorrhea and recently had developed ideas of self-harm and grandiose delusions which warranted readmission. Of note, additional history revealed that he had been hospitalized 30 years prior for similar manic symptoms, but was discharged without a definitive diagnosis there were no recurrences of psychiatric symptoms until the current episode.

At initial evaluation, the patient was afebrile and vital signs were stable (Table 1). In addition, the patient was oriented to person, place, and time, but he was hyperalert and restless. Although he was cooperative, his speech was loud, jittery, reiterative, logorrheic, and abnormally fast. He presented with an inappropriately elevated mood commenting he was "better than ever" and with grandiose delusions remarking he was "like God" and "[had] the cure for the COVID-19 pandemic." He also experienced delusions characterized by a belief that the government and healthcare workers sought to persecute him for his reportedly extensive knowledge about COVID-19. The patient was evaluated by psychiatry, who diagnosed him with a moderate manic episode, and he was initially treated with intramuscular diazepam 5 mg. A head magnetic resonance imaging (MRI) study showed no abnormalities, and cerebrospinal fluid

(CSF) analysis was unremarkable for abnormalities in cell count or protein. CSF and repeat samples from the nasopharynx were negative for SARS-CoV-2 by rRT-PCR.[5,6]

Of note, given that it was not possible to hospitalize him due to administrative limitations, he was discharged with a diagnosis of bipolar I disorder. He was treated on an outpatient basis with risperidone 2 mg orally every 12 h, valproic acid 500 mg orally every 12 h, and clonazepam 2 mg orally every 24 h. He adhered to this medical regimen and his symptoms resolved completely 1 month after discharge.

2.2 | Case 2

A 48-year-old male with a history of essential hypertension presented to the UHC with 7 days of fever (between 38.3°C and 38.7°C), dyspnea, headache, and dry cough. Hypoxemia (pulse oxygen saturation: 87%) was evident on admission, and SARS-CoV-2 infection was confirmed by rRT-PCR on a nasopharyngeal specimen (Day 0). The patient also had an elevated lactate dehydrogenase (LDH: 320 U/L) and complete blood count revealed moderate thrombocytopenia (55 000/µl). Renal and hepatic diagnostic laboratory values were within normal limits, and human immunodeficiency virus (HIV) serology was negative. The patient was admitted and required supplemental oxygen. He was started on DX 8 mg daily for 15 days, with resolution of symptoms at Day 15, at which point he was discharged.

At Day 30, the patient was brought back to the emergency room due to increased psychiatric symptoms, including a significant decrease in sleep in the 7 days prior, a broad affect, recent incursion in risky economic activities, and high levels of anxiety. On neuropsychiatric exam, the patient demonstrated psychomotor restlessness, rapid speech with tangential thought, tachypsychia, pleasurable hyperthymia, and delusional ideas of religious-mystical content. He was admitted with the initial diagnosis of a moderate manic episode with anxiety. The patient had a mild elevation of LDH (260 U/L) and mild elevation of C-reactive protein (CRP: 1.4 mg/dl) (Table 1). Otherwise, all other diagnostic laboratory values as well as head computed tomography (CT) were unremarkable. The patient received outpatient treatment of risperidone 2 mg orally every 12 h and clonazepam 2 mg orally daily. He progressively improved over the course of treatment, with complete resolution of symptoms 1 month after initiation of medical therapy.

2.3 | Case 3

A 25-year-old male with no known medical history presented to the military hospital with 3 days of dry cough, headache, and fever (between 38 °C and 38.7 °C). At presentation (Day 0), he was afebrile (36.5 °C) with stable vital signs. On neuropsychiatric exam, the patient was fully alert, auto- and allopsych oriented, with no motor or sensitive deficits, and no signs of meningeal irritation. SARS-CoV-2 testing of a nasopharyngeal specimen was confirmed by rRT-PCR,

Patient	#1	#2	#3	#4	#5
Sociodemographic characteristics					
Age	58	48	25	34	26
Gender	Male	Male	Male	Male	Male
Marital status	Married	Married	Single	Married	Single
Occupation	Pilot	Merchant	Military	Military	Military
Severity of COVID-19	Mild	Severe	Mild	Mild	Mild
Treatment for COVID-19					
Chloroquine	Yes	No	Yes	Yes	Yes
Dexamethasone	No	Yes	No	Yes	N
Day with psychiatric symptoms (relative to COVID-19 diagnosis)	56	30	17	11	12
Neuropsychiatric exam findings					
Neurological exam	Normal	Normal	Normal	Altered	Normal
Delusions	Yes	Yes	Yes	Yes	Yes
Hallucinations	No	No	Yes	Yes	Yes
Disorganized speech	Yes	Yes	No	No	Yes
Altered affect	Yes	Yes	Yes	No	Yes
Vital signs					
Oxygen saturation (%)	98	96	96	97	98
Temperature (°C)	36.5	36.9	37	36.5	36.5
Blood pressure (mmHg)	130/90	135/80	120/80	125/80	130/80
Heart rate (bpm)	98	102	96	95	109
Laboratory diagnostics					
Leukocytes ($4.3–12.3 \times 10^3/\mu l$)	7.2	8.2	12.1	18.1	10.2
Hemoglobin (13.6–17.2 g/dl)	14.1	15	13.2	14.8	13.1
Platelets ($150–388 \times 10^3/\mu l$)	182	148	380	468	263
Neutrophils (%)	70	90	75	70	80
Lymphocytes (%)	24	7	20	20	17
Erythrocyte sedimentation rate (0–22 mm/h)	10	15	15	15	20
Glucose (70–110 mg/dl)	87	92	75	84	70
Creatinine (0.4–1.4 mg/dl)	0,9	0.8	1.05	1.02	1.3
AST (8–48 U/L)	23	18	NA	37	19
ALT (7–55 U/L)	30	26	NA	107	13
Sodium (136–145 mg/dl)	142	138	135	133	NA
Potassium (3.5–5.2 mg/dl)	3.8	3.7	3.9	4.2	NA
Chlorine (98–108 mg/dl)	100	102	99	95	NA

TABLE 1 Sociodemographic and clinical characteristics of COVID-19 patients with psychiatric symptoms

Patient	#1	#2	#3	#4	#5
Lactate dehydrogenase (0–248 U/L)	252	260	NA	270	NA
C-reactive protein (0–1 mg/dl)	0.6	1.4	NA	0.03	1.2
Neurological studies					
Brain magnetic resonance	Normal	NA	NA	Normal	NA
Head computed tomography	NA	Normal	Normal	NA	Normal
Electroencephalogram	NA	NA	NA	Normal	NA
Cerebrospinal fluid analysis	Normal	NA	NA	NA	NA
Neuropsychiatric diagnosis	Bipolar I disorder	Manic episode	Major depressive episode with psychotic features	Brief psychotic disorder	Brief psychotic disorder

Abbreviations: COVID-19, coronavirus disease 2019; mmHg, millimetres of mercury; bpm, beats per minute; mm/h: millimeters per hour; mg/dl: miligrams per deciliter; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not available.

and the patient was discharged to be managed as an outpatient with CQ 300 mg orally every 12 h for 10 days and azithromycin 500 mg orally every 24 h for 7 days. He demonstrated clinical improvement at Day 10.

At Day 17, he returned to the military hospital with dysphoric affect (e.g., easily crying), ideas of death, anhedonia, conciliation insomnia, psychomotor restlessness, delusional ideas of persecution, and visual and auditory hallucinations. At presentation, his vital signs were stable, and complete blood count, hepatic and renal function tests, HIV serologies, and head CT were unremarkable (Table 1). He was admitted with the diagnosis of major depressive episode with psychotic features. Pharmacologic treatment was indicated on an outpatient basis and included olanzapine 5 mg orally every 12 h, paroxetine 20 mg orally daily, alprazolam 0.5 mg orally every 12 h, zolpidex 10 mg orally every 12 h. Despite reported adherence to the medical treatment, at 1-month follow-up (Day 47), the patient presented with delusional ideas of harm and visual hallucinations, for which his medical treatment was adjusted to sertraline 50 mg orally every 24 h, risperidone 0.5 mg orally every 12 h, and alprazolam 0.5 mg every 12 h. Adherence to this regimen resulted in the resolution of symptoms at subsequent follow-up (Day 90).

2.4 | Case 4

A 34-year-old male, with no history of mental disease or comorbidities, consulted to the Military Hospital for 3 days of cough, headache, and respiratory distress. On initial assessment, the patient was afebrile (37 °C) and vital signs were stable (Day 0). On neuropsychiatric exam, the patient was fully alert, auto- and allopsychically oriented, with no motor or sensitive deficit, and no signs of meningeal irritation. A confirmatory diagnosis of SARS-CoV-2 infection was obtained by rRT-PCR testing of a nasopharyngeal specimen. He was hospitalized for 6 days for isolation, where he received CQ 300 mg every 12 h and DX 8 mg intravenously every 24 h, each for 6 days. At Day 6, his symptoms resolved, and he was discharged.

However, at Day 11, he was brought in by family to the emergency service for evaluation of new psychiatric symptoms including disorganized and disruptive behavior, verbal and physical heteroaggression toward third parties, allopsychic disorientation, psychomotor restlessness, thought blockage, mystical-religious and persecutory delusions, and conciliation insomnia. At this presentation, vital signs were stable (Table 1). Initial laboratory studies demonstrated leukocytosis ($18 \times 10^3/\mu l$) and mild transaminitis (ALT: 107 U/L; AST: 37 U/L). Of note, HIV serology, head MRI, and electroencephalogram were unremarkable (Table 1). The patient was admitted with a diagnosis of brief psychotic disorder with symptoms of schizophrenia, and risperidone 2 mg orally per day and biperiden 2 mg orally every day were indicated. After 5 days of pharmacologic treatment, the patient was discharged home to complete outpatient treatment. At Day 18, the patient's neuropsychiatric symptoms began to resolve and the dose of the medications was tapered through Day 32, when he completed treatment.

2.5 | Case 5

A 26-year-old male with no history of mental disease presented with 4 days of headache, dry cough, fatigue, and fever (between 38.5 °C

and 39 °C). On initial assessment (Day 0), the patient was afebrile (36.2 °C), and his vital signs were stable. On neuropsychiatric exam, the patient was fully alert, auto- and allopsychic oriented, with no motor or sensitive deficit, and no signs of meningeal irritation. SARS-CoV-2 infection was confirmed by rRT-PCR testing of a nasopharyngeal specimen, and the patient was treated with CQ 300 mg orally every 12 h as an outpatient, with improvement of symptoms at Day 5.

However, at Day 12, he presented to the emergency room with disruptive behaviors and aggression to external objects/people. He was tachycardic (109 bpm) and presented with delusional ideas of harm and jealousy, as well as audiovisual hallucinations. Other than a borderline CRP elevation (1.2 mg/dl), diagnostic laboratory testing was unremarkable, and his remaining vital signs were stable (Table 1). Given these symptoms, the patient was admitted with a diagnosis of brief psychotic disorder. During his 31-day hospitalization (Days 12–43), he was treated with haloperidol 10 mg intramuscularly every 12 h for 72 h, and valproic acid 500 mg orally every 12 h. After improvement of symptoms at Day 43, outpatient pharmacologic treatment was adjusted to risperidone 2 mg orally every 12 h and clonazepam 2 mg orally daily. Continued, progressive improvement was evident on periodic evaluation (every 15 days) with a complete resolution of symptoms within the following 3 months.

3 | DISCUSSION

In a patient exhibiting psychiatric symptoms consistent with acute manic, depressive, or psychotic features, current diagnostic criteria require the exclusion of the pathophysiologic effects of a toxic substance, medication, or a medical condition. Each of the aforementioned cases demonstrate multiple psychiatric symptoms that are consistent with the various diagnostic criteria of bipolar I disorder (case #1, #2), major depressive episode (#3), and brief psychotic disorder (#4, #5). Although the natural course of psychotic diseases is a potential explanation for such manifestations, both SARS-CoV-2 infection (and neuroinflammatory sequelae) and COVID-19 treatments, themselves, must be considered as potential catalysts for new-onset neuropsychiatric symptoms in COVID-19 patients.

Other human coronaviruses (HCoV) have previously been shown to have neuropathologic potential. Indeed, acute SARS-CoV infection has been linked to affective psychosis[7,8] and organic mania and hallucinosis,[9] while the more ubiquitous seasonal OC43 and 229E subtypes have been associated with chronic demyelinating diseases such as multiple sclerosis.[10,11]

Currently, studies that investigate the psychiatric impacts of SARS-CoV-2 infection are largely limited to surrogate studies investigating psychiatric symptoms in SARS and Middle East respiratory syndrome (MERS) infection,[12] one national surveillance study of 153 patients,[13] and case reports.[14,15] For example, a recent report describes new-onset severe anxiety, agitation, paranoia, and disorganized thinking in three SARS-CoV-2 infected patients undergoing nonsteroidal treatment in the absence of respiratory or other neurologic symptoms.[16] Similar reports were described in an actively SARS-CoV-2-positive patient[17] and a convalescent COVID-19 patient[18] each without prior psychiatric medical history; although corticosteroid treatment was also a potential trigger in the latter. These studies complement the 10 of 153 COVID-19 patients in the United Kingdom who were reported to have new-onset psychosis.[13]

The COVID-19 pandemic may impact mental health both indirectly, due to increased and prolonged psychosocial stress and through more direct effects of SARS-CoV-2 infection. Although psychotic symptoms have been described in only a few acute or convalescent COVID-19 patients,[12] multiple reports indicate the risk of developing new psychiatric symptoms or exacerbating preexisting mental disorders[3] has increased during COVID-19 outbreaks. Recent studies have reported significant prevalence rates of posttraumatic stress disorder, major depressive disorder, and generalized anxiety disorders[19] in patients with COVID-19. SARS-CoV-2-infected patients may experience neuropsychiatric and encephalopathic symptoms including agitation, confusion, dysexecutive syndrome, delirium,[20] acute mania,[21] or acute psychosis.[16,17]

In this case series, we report several scenarios which highlight the onset of neuropsychiatric symptoms due to direct central nervous system (CNS) infection by SARS-CoV-2, indirect neuroinflammation in the setting of SARS-CoV-2 infection, chloroquine and/or corticosteroid neurotoxicity, or a combination of the aforementioned.

3.1 | Direct or indirect injury caused by SARS-CoV-2 infection

The neurologic pathogenesis and neurotropic potential of SARS-CoV-2 remain unclear. In addition to the wide distribution in the lungs, intestines, endothelium, and kidneys, the host cell receptor for SARS-CoV-2 — angiotensin converting enzyme 2 (ACE2)— has been identified in neurons, glia, and blood–brain barrier (BBB) capillary cells in the CNS.[22,23] In addition, neuropilin-1 (NRP-1), which has been described as an alternative viral receptor to host cell entry,[24,25] is found in the olfactory epithelium.[24] Given that SARS-CoV-1 has been shown to enter CNS cells,[26] it is attractive to speculate the same ability of SARS-CoV-2 particularly because of its high sequence homology to the SARS-CoV-1 receptor-binding domain.[27] Indeed, SARS-CoV-2 has demonstrated in vitro infectivity of human brain organoids[23] and in vivo infectivity of mice expressing human ACE2.[28] Moreover, the presence of blebbing viral particles in BBB endothelial cells and adjacent frontal lobe neurons suggests that SARS-CoV-2 could also disseminate hematogenously via paracellular, transcellular, or "trojan horse" mechanisms to reach the CNS and cause direct cytopathic effects.[29] Furthermore, reports of retrograde axonal transport of several coronaviruses, such as HCoV-OC43 through the olfactory bulb, may explain the early olfactory and gustatory deficits in COVID-19 patients and provide another potential direct entry point to the CNS.[30,31]

Additionally, neuroinflammation secondary to viral infection is a plausible etiology for CNS cellular damage and neuropsychiatric pathogenesis. For example, in patients infected with arboviruses (e.g.,

Zika virus, Chikungunya virus) who presented with new cognitive impairment or precipitation of manic episodes,[32] severe inflammatory systemic response (pro-inflammatory molecules in the CNS) and postinfectious, immune-mediated phenomena (presence of brain-reactive antibodies) appear to be the main factors implicated in the pathophysiology of viral-related neuropsychiatric symptoms. Similarly, overproduction of pro-inflammatory cytokines (cytokine storm) and exacerbated cytotoxicity has been described in COVID-19 patients,[33] which have been associated with the onset of neurological and neuropsychiatric symptoms.[34] This pathogenic mechanism parallels the increased levels of acute-phase reactants (e.g., CRP) seen in previous case reports[15,16] as well as two of the five patients presented (#2, #5) in this case series.

3.2 | Chloroquine neurotoxicity

Chloroquine (CQ) has been used historically as an antimalarial and repurposed for the management of several rheumatoid autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus). It emerged as a therapeutic option during the COVID-19 pandemic because of its anti-inflammatory and potential antiviral effects.[35] However, current evidence shows that the minimal and inconsistent benefit for mortality and other outcomes of COVID-19 patients treated with CQ is outweighed by potentially life-threatening cardiovascular and neurologic adverse effects causing the Food and Drug Administration to retract CQ's emergency use authorization for the treatment of COVID-19 patients in the United States.[36] Neuropsychiatric symptoms, including psychosis, grandiose delusions, paranoia, hallucinations, and even suicidality, have been described up to 8 weeks after ceasing CQ treatment.[37,38] The pathogenesis of CQ-induced psychosis may be mediated—at least in part—by its dopaminergic, serotoninergic, and antimuscarinic effects in the CNS.[39] Cases of CQ-induced mania may present as drug-induced psychosis, or behave more like an affective disorder.[40] Although most psychiatric side effects of CQ and hydroxychloroquine have been described in the setting of rheumatologic disease treatment,[38] two case reports describe psychosis and anxiety in COVID-19 patients treated with CQ,[41] and a global pharmacovigilance study found the use of hydroxychloroquine was associated with an increased risk of psychiatric disorders.[42] Interestingly, in four of the five patients presented (#1, #3, #4, and #5), the rapid onset of symptoms after initiation of the drug and remission shortly after discontinuation, support CQ as a potential trigger for their neuropsychiatric symptoms; however, the direct impacts of direct CNS infection by SARS-CoV-2 or the indirect effects of neuroinflammation secondary to COVID-19 cannot be excluded.

3.3 | The role of dexamethasone

In the hyperinflammatory setting of SARS-CoV-2 infection, corticosteroids have been proposed as a component of treatment.

Although multiple studies have demonstrated their utility in treatment in the inpatient setting,[43,44] its use has the potential to induce acute psychosis.[45,46] Corticosteroid-induced psychosis is a rare but well-known disorder classified as a form of substance/medication-induced psychotic disorder in the "Diagnostic and Statistical Manual of Mental Disorder".[47] Its pathophysiology remains poorly understood, but it is presumed to originate from an imbalance between glucocorticoid stimulation and mineralocorticoid receptor stimulation[48] and may be the result of glutamate-induced neuronal toxicity.[49] The majority of these patients usually develop symptoms within the first 2 weeks after initiation of corticosteroid therapy and cases are usually self-remitting after discontinuation of therapy, similar to what we observed in two of our cases (#2 and #4).

Overall, the psychiatric impacts of corticosteroids in COVID-19 patients are minimal. Most studies refer to the psychiatric side-effects of steroid use in SARS and MERS infection as a surrogate for similar sequelae in SARS-CoV-2 infection. For example, a meta-analysis by Rogers et al. early in the COVID-19 pandemic found one report of steroid-induced mania and psychosis in 13 (0.7%) of 1744 patients with acute SARS and MERS infection.[12] However, psychiatric symptoms in COVID-19 patients undergoing steroid treatment have not been well described in the literature. Thus, further studies are warranted to delineate the complex etiologist of neuropsychiatric disease in SARS-CoV-2-infected patients.

4 | CONCLUSION

An increased risk for new-onset or exacerbated neuropsychiatric disease has been described in communities experiencing COVID-19 outbreaks across the globe. Immediate and long-term neuropsychiatric complications following SARS-CoV-2 infection are currently unknown. Thus, further investigations are warranted to understand the viral, immunologic, and pharmacologic drivers of psychiatric disease pathogenesis in SARS-CoV-2-infected patients. With current guidelines advising against the use of chloroquine and hydroxycloroquine in hospitalized and nonhospitalized patients, and the potential risks of dexamethasone for developing neuropsychiatric complications, therapeutic decision-making should follow balancing risk/benefits to the patient.

CONFLICT OF INTEREST
All authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS
Data collection: David A. Forero-Peña, Iriana Paola Mozo-Herrera, Iván Bolívar Collado-Espinal, Joselyn Páez-Paz, Carlos Ferro, Carlos Morantes. *Analysis and interpretation*: David A. Forero-Peña, Matthew M. Hernandez, Iriana Paola Mozo-Herrera, Iván Bolívar Collado-Espinal, Joselyn Páez-Paz, Carlos Ferro, Carlos Morantes, David M. Flora-Noda, Andrea L. Maricuto, Viledy L. Velásquez, Natasha A. Camejo-Avila, Emilia M. Sordillo, Lourdes A. Delgado-Noguera, Luis A. Perez-Garcia, María Eugenia Landaeta, Alberto E. Paniz-Mondolfi. *Writing/Drafting*:

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ETHICS STATEMENT
Informed consent was obtained from all patients.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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