

First Case of Evidence of Rare Autoimmune Encephalitis in Patient with Severe Sars-Cov-2 Pneumonia and History of Chronic Alcoholism

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Abstract

The novel coronavirus disease (COVID-19) caused by the acute and atypical respiratory syndrome coronavirus 2 (SARS-CoV-2) has been declared a global pandemic by the World Health Organization (WHO) on the 11th of March. At 8th July 2021, globally infections are crossing 185 million and there are over 4.000.000 fatalities. Concerning central nervous system involvement, a wide spectrum of non- bacterial encephalitis secondary to a direct viral damage hyper inflammation syndrome have been described. Conversely, only few cases of encephalitis due to an antibody-mediated mechanism have been reported and even fewer of autoimmune limbic encephalitis. These cases have been mostly described within case series involving other types of encephalitis or encephalopathies, without receiving a specific attention. It is known that neurons and glia express the putative SARS-CoV-2 receptor angiotensin converting enzyme 2, and that the related coronavirus SARS-CoV (responsible for the 2003 SARS outbreak) can inoculate the mouse olfactory bulb [5]. If SARS-CoV-2 can enter the central nervous system (CNS) directly or through haematogenous spread, cerebrospinal fluid (CSF) changes, including viral RNA, IgM, or cytokine levels, might support CNS infection as a cause for neurologic symptoms. We present an Italian patient with Severe Case of SARS-CoV-2 disease, chronic alcoholism with evidence of autoimmune encephalitis.

Keywords: Sars-Cov 2; Severe Pneumonia; Autoimmune Encephalitis; chronic alcoholism

Background

The novel coronavirus disease (COVID-19) caused by the acute and atypical respiratory syndrome coronavirus 2 (SARS-CoV-2) has been declared a global pandemic by the World Health Organization (WHO) on the 11th of March. At 8th July 2021, globally infections are crossing 185 million and there are over 4.000.000 fatalities [1]. Concerning central nervous system involvement, a wide spectrum of non- bacterial encephalitis secondary to a direct viral damage hyper inflammation syndrome have been described [2]. Conversely, only few cases of encephalitis due to an antibody-mediated mechanism have been reported and even fewer of autoimmune limbic encephalitis [3].

These cases have been mostly described within case series involving other types of encephalitis or encephalopathies, without receiving a specific attention. It is known that neurons and glia express the putative SARS-CoV-2 receptor angiotensin converting enzyme 2, and that the related coronavirus SARS-CoV (responsible for the 2003 SARS outbreak) can inoculate the mouse olfactory bulb [4,5]. If SARS-CoV-2 can enter the central nervous system (CNS) directly or through haematogenous spread, cerebrospinal fluid (CSF) changes, including viral RNA, IgM, or cytokine levels, might support CNS infection as a cause for neurologic symptoms. We present an Italian patient with Severe Case of SARS-CoV-2 disease, chronic alcoholism with evidence of autoimmune encephalitis.

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Description

Our Italian patient 66-year-old, male, developed fever up to 38.9 degrees C, asthenia, myalgia, dyspnea, poorly cough, seizure, headache, visual disturbances and confusional state on 4 April 2021. In the Hospital of Alghero, Sardinia, Italy he was admitted immediately after computed tomography scan (CT scan) imaging of his chest showed multiple and bilateral ground-glass opacities located in both subpleural and apico-basal spaces (especially on the left) and extensive left spontaneous pneumothorax with subtotal lung collapse. Nasopharyngeal swab specimens were collected to detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleic acid. The swab specimens were tested by real-time reverse transcriptase-polymerase chain reaction; a

positive result was received 8 hours later on 4 April 2021. Our patient was diagnosed with COVID-19. He received 100 mg Remdesivir (Veklury) tablets orally, 3 times daily, Tocilizumab was given I.V.400 mg single dose for “cytokine storm”, O₂ Therapy; Proton Pump Inhibitors (pantoprazole 40 mg, 2 times daily), steroid (dexamethasone 6 mg for 10 days), Meropenem 2 g tid, Acyclovir 750 mg tid, Midazolam 15 mg 3 f in 500 cc of SF in continuous infusion, chlorpromazine 50 mg bid, flecainide 100 mg bid, sotalol 80 mg/die, allopurinol 300 mg/die, rehydration therapy. Concomitant pathologies: arterial hypertension, dyslipidaemia, functional monorene, gouty arthropathy, prostatic hypertrophy, spinal canal stenosis (recent decompression and stabilization of L5-S1).

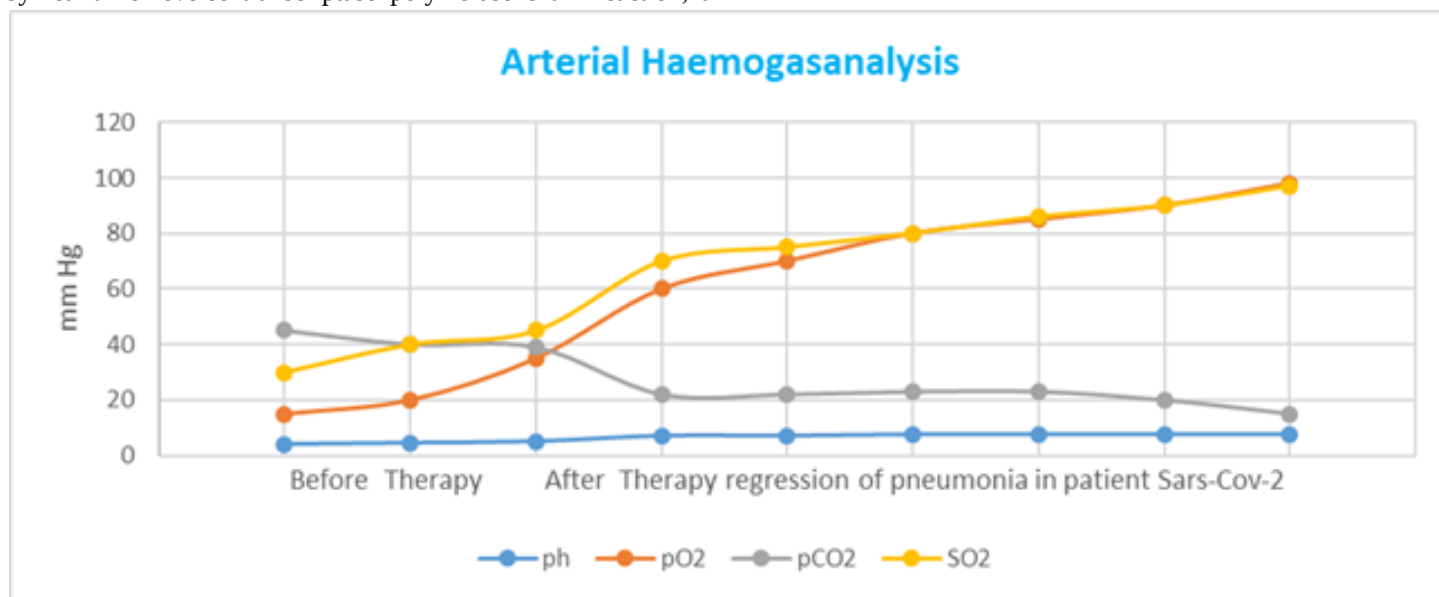


Figure 1: Arterial Haemogasanalysis.

One week after admission, on 15 April, 2021 our patient show an important confusional state and psychomotor agitation that resulted in bed restraint and sedation under continuous infusion with midazolam, as per Neurological Consultation for suspect of encephalitis. Control Computerized tomography scan performed: uncooperative patient, examination significantly hampered by movement artifacts. Not evident images referable to encephalic lesions of hemorrhagic nature or gross encephalic lesions of ischemic nature. The patient showed a severe agitation syndrome associated with mutism; he was uncooperative and unable to carry out even simple orders if not stimulated. Positive palmomental and glabella reflexes with moderate nuchal rigidity were detected, with no focal signs at the neurological examination. Hematochemical examinations: neutrophilic leukocytosis, increase of: C - reactive protein, procalcitonin, fibrinogen, ferritin, urea, LDH, GT, blood glucose, cholinesterase, increased

D-dimer (968ng/ml) but normal concentrations of C-reactive protein. Emogasanalysis and clinical course: (Figure 1).

07/04 FiO₂ 21% pH 7.44, pO₂ 62 mmHg, pCO₂ 37 mmHg P/F 295

08/04 Ventimask FiO₂ 31% pH 7.45, pO₂ 76 mmHg, pCO₂ 36 mmHg P/F 245

09/04 Ventimask FiO₂ 31% pH 7.38, pO₂ 71 mmHg, pCO₂ 35 mmHg P/F 229

10/04 Ventimask FiO₂ 31% pH 7.43, pO₂ 89 mmHg, pCO₂ 36 mmHg P/F 287

12/04 Ventimask FiO₂ 31% pH 7.33, pO₂ 85 mmHg, pCO₂ 39 mmHg P/F 274

10/04 Ventimask FiO₂ 31% pH 7.43, pO₂ 89 mmHg, pCO₂ 36 mmHg P/F 287

14/04 Ventimask FiO₂ 28% pH 7.49, pO₂ 66 mmHg, pCO₂ 36 mmHg P/F 236

16/04 Ventimask FiO₂ 28% pH 7.48, pO₂ 77 mmHg, pCO₂ 34 mmHg P/F 275

18/04 Ventimask FiO₂ 28% pH 7.45, pO₂ 92 mmHg, pCO₂ 37 mmHg P/F 329

25/04 Ventimask FiO₂ 40% pH 7.42, pO₂ 75.2 mmHg, pCO₂ 26.5 mmHg, Lac 10 mg/dl P/F 307 Lumbar puncture:

Cerebrospinal fluid: cytochemical examination: Glucose 68 mg/dl [40-70]; Absent cells, Clear appearance: Colorless color, Chlorine 130, Protein 50 mg/dl [12-40].

Molecular test FilmArray Meningitidis/Encephalitis panel (bacteria, viruses, yeasts) NEGATIVE EBV-DNA negative; HSV2-DNA negative; HSV1-DNA negative; CMV-DNA negative; Negative Sars-CoV-2.

Cerebrospinal fluid culture test negative. On 26 April 2021 Magnetic Resonance Image and electroencephalogram not performed: death of the patient.

Severe Autoimmune encephalitis in a patient devastated for Interstitial Pneumonia and Chronic Alcoholism?

Discussion

We are still learning about all the neurological complications of COVID-19. Encephalitis appears to occur in multiple ways. There have been case reports of SARS-CoV-2 detection within the spinal fluid and patients presenting with an inflammatory syndrome of the brain. COVID-19 is associated with a high state of inflammation throughout the body. This also adversely affects the brain. There is speculation that the blood vessels that supply blood to the brain become inflamed and result in brain injury in terms of stroke and secondary tissue dysfunction. There also may be inflammation that causes secondary damage to the brain as the immune system fights the virus and there is cross-reactivity to the brain itself. Our case is characterized by evidence of autoimmune encephalitis in the context of severe COVID-19 pneumonia and Chronic Alcoholism. Clinically, the patient presented with various neuropsychiatric symptoms, which were reported before in other COVID-19 patients with encephalopathy [5]. Neither SARS-CoV-2 itself nor antibodies against the virus were found positive in the CSF, precluding direct viral CNS infection. Comprehensive laboratory tests ruled out antineuronal antibodies as well as common infectious causes of encephalitis, altogether supporting the diagnosis of parainfectious autoimmune encephalitis. In addition, the diagnostic criteria for possible autoimmune encephalitis as proposed. Were met [6]. The use of technology called next-generation sequencing of metagenomics has allowed the identification of infectious causes of encephalitis that were not previously considered. A new form of autoimmune encephalitis that was previously unrecognized is also being recognized. Being able to reliably distinguish between infectious and autoimmune encephalitis even a decade ago was extremely difficult; this is important because treatment will differ greatly

between the two. One requires the use of antimicrobial drugs while the other relies on immunomodulatory drugs. With the ability to more accurately diagnose the cause of encephalitis, patients receive the appropriate treatment and have a better chance of recovery [7]. Some of the diagnostic tests may take time to accurately diagnose encephalitis. There is a saying in the stroke world that time is brain; the same is true for encephalitis. The longer the diagnosis is delayed, the more vulnerable the brain is to further injury. It would serve to have timely diagnostics at the point of care that can quickly provide physicians and patients with the cause of encephalitis and also to benefit from more targeted treatments. For some forms of viral encephalitis, we can only provide supportive care because we do not have a drug that can actively reduce viral replication. There are still a number of unmet needs [8]. We need prospective studies of treatment options and additional patient characteristics to further understand the variables associated with COVID-19-associated death in patients with Autoimmune Encephalopathy.

Conclusion

Although a very limited number of autoimmune have been described until now, it is important to consider the possibility of an autoimmune process also in the setting of COVID-19 infection, in particular if neurological impairment appears late, when respiratory symptoms are resolving. In these cases, managing an early diagnostic set-up with Cerebrospinal fluid analysis, electroencephalogram (EEG), and brain imaging, represents the best diagnostic strategy, in order to avoid unnecessary delays and promptly start the appropriate treatments. Future studies oriented towards biomarkers identification may help to correctly identify the pathophysiological mechanisms underlying the wide spectrum of encephalitis and better clarify the pathological process of LE encephalitis in the setting of COVID-19.

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SUNTEXT REVIEWS

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