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Post Covid Auto Immune Mediated Encephalopathy by Caspr2 Auto-Antibody: The Report of Neurological Division of "Carlo Poma Civil" Hospital of Mantua

Mirko Avesani[1], Alfonso Ciccone[2]
[1,2] Division of Neurology, Civil Hospital of Mantua
[1]University of Padua

INTRODUCTION

A recent cross-sectional study (Liu, 2021) suggests that SARS-CoV-2 infection has a potential long-term impact on the cognition of patients: we have to face with post covid syndrome and with long covid syndrome, the first characterized by symptoms in regression after an year by infection, the last with persisting symptoms after an year by infection. As the COVID-19 pandemic is still raging in many countries and is expected to last for a long period, the long-term cognitive sequelae may become a major public health issue long after the pandemic has ended. Longitudinal studies to follow up patients who have recovered from COVID-19 are necessary for better understanding the long-term cognitive consequences of COVID-19, particularly among those who have recovered from severe disease.

But these are not the unique problems of the so called NEUROCOVID. Neuromuscular manifestations of new coronavirus disease 2019 (COVID-19) infection are frequent, and include dizziness, headache, myopathy, severe (also axonal) Guillain Barrè Syndrome and olfactory and gustatory disturbances. Patients with acute central nervous system disorders, such as delirium, impaired consciousness, stroke and convulsive seizures, have a high mortality rate (Shimohata, 2022).

Another severe condition is rappresented by autoimmune encefalopathies COVID related.

The encephalitis/encephalopathy that causes consciousness disturbance and seizures can be classified into three conditions, including direct infection with the SARS-CoV-2 virus, encephalopathy caused by central nervous system damage secondary to systemic hypercytokinemia (cytokine storm) and autoimmune-mediated encephalitis that occurs after infection.

This particular form of encephalopathy, that is the last, is still today very few known. In literature there are few studies.

A study (Hilado, 2022) reports the cases of autoimmune-mediated encephalitis in three pediatric patients. These 3 cases provide evidence that antibody-negative autoimmune encephalitis could be a potential complication following SARS-CoV-2 infection in children. Although a temporal association with SARS-CoV-2 infection as evidenced by SARS-CoV-2 serum antibodies certainly does not imply a causal link to the subsequent autoimmune encephalitis diagnosed and treated in these patients, the absence of any other clear infectious or autoimmune source of central nervous system disease with the excellent, timely, and sustained response to steroids without remission or recurrence of neurologic dysfunction strongly point to this diagnosis of exclusion. As the pandemic continues, providers should consider that a postinfectious autoimmune-mediated encephalitis may be the sole manifestation following SARS-CoV-2 infection. Recognizing this potentially disabling complication should prompt consideration of immune modulating medications like high-dose corticosteroids once other etiologies have been ruled out.

Another study of 2021 (Nersejan), on adult patients, systematically described central (CNS) and peripheral (PNS) nervous system complications in hospitalized COVID-19 patients.

The authors conducted a prospective, consecutive, observational study of adult patients from a tertiary referral center with confirmed COVID-19. All patients were screened daily for neurological and neuropsychiatric symptoms during admission and discharge. Three-month follow-up data were collected using electronic health records. They classified complications as caused by SARS-CoV-2 neurotropism, immune-mediated or critical illness-related. From April to September 2020, they enrolled 61 consecutively admitted COVID-19 patients, 35 (57%) of whom required intensive care (ICU) management for respiratory failure. Forty-one CNS/PNS complications were identified in 28 of 61 (45.9%) patients and were more frequent in ICU compared to non-ICU patients. The most common CNS complication was encephalopathy (n = 19, 31.1%), which was severe in 13 patients (GCS ≤ 12), including 8 with akinetic mutism. Of 41 complications in total, 3 were para/post-infectious, 34 were secondary to critical illness or other causes, and 4 remained unresolved. Cerebrospinal fluid was negative for SARS-CoV-2 RNA in all 5 patients investigated. In Conclusion, CNS and PNS complications were confirmed as common in hospitalized COVID-19 patients,

particularly in the ICU, and often attributable to critical illness. When COVID-19 was the primary cause for neurological disease, no signs of viral neurotropism were detected, but laboratory changes suggested autoimmune-mediated mechanisms.
In then end, the last study published in 2021 (Kaur, 2021), is a case report, describing catatonia as a possibile result of new-onset COVID infection, in a 59 years old man. This patient did not have a previous history of catatonia and PCR COVID testing was negative on admission. He developed catatonia and delirium within a week of hospitalization and the second PCR test at that time was positive. So, the author concluded that The neuropsychiatric manifestations of COVID-19 may include delirium, depression, anxiety, insomnia, agitation, and catatonia (Kumar, 2021). Catatonia can present in COVID-19 patients without prior history of neuropsychiatric disordera (Scheiner, 2021).

THE EXPERIENCE OF NEURO-COVID DIVISION OF "CARLO POMA" CIVIL HOSPITAL OF MANTUA (ITALY).
In our Neuro Covid Division, we face several auto-immune mediated encefalophaties.
The most significative post covid autoimmune encephalopathy was related to CASPR2 autoantibody. A rare antibody to detect in an auto-immune mediated encefalopathy.
This case reports the history of a patient admitted to our division after classical interstitial pneumonia caused by sars-cov2 infection.
After healing by pneumonia, he presented himself as affected by sub-acute severe neuropsychiatric syndrome. He was deprived by any verbal and behavioural inhibition, while, previously, he has always demonstrated himself as a moderate man.
The first Standard MRI of the brain (fig. 1) was negative for vascular or inflammatory diseases.

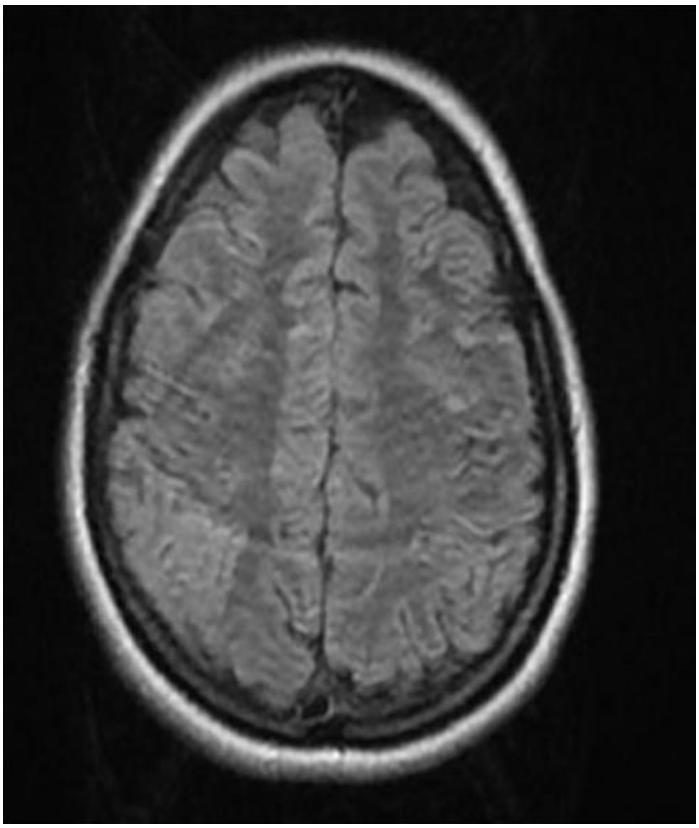

Fig. 1. First MRI of the brain

But we must consider that the MRI was performed in the first days since the patient presented himself as affected by this mental disorder and in this period we can face a false negative MRI of the brain. MRI of the brain, usually, in the case of autoimmune encephalopathies becomes positive after weeks.
But we were directed towards this hypothesis because the patient did not present particular deficit under the neurological point of view. The patient, furthermore, was afebrile.
So, the clinical manifestations were only psychiatric, with a sub-acute onset.

We discussed the case with psychiatric colleagues, that, at the moment, did not consider the patient psychiatric unless every clear organic disease was excluded, as indicated by DSM-V.

So we proceeded with lumbar puncture. Standard results of liquor alredy turned out suggestive for an inflammatory process, because the proteins were very elevated (120 mg/dL), and there were 5 white blood cells (all lymphocytes). This was the proof of a inflammatory process in the brain.
The meningo-encephalithis pannel (that is, the research of a bacterial or viral infectious) was all negative.
The unique hypothesis on the field was a form of autoimmune inflammatory disease of the brain.
So, ex adjuvantibus, we treated the patient with IgG intravenously at standard dosage (0.4 gr/kg/die for five days) and then with steroidal therapy (methylprednisolone, 1 gr/die intravenously for other five days, and then dexamethasone per os, to climb for a month).
The patient clearly recovered himself and his psychiaric disorder disappeared. This improvement confirmed our hypothesis.
But the definitive confirmation arrived from our Laboratory of Neuropathology. Immunohistochemistry analysis detected the presence (high degree of positivity: +++) on liquor of autoantibodies anti-CASPR 2 (contactin-associated protein like 2).
Other positivity was detected, but only on serum, for auto-antibodies anti VOCs (Voltage Operated Channels) for potassium (K), with an high degree of positivity (274,00 pmol/L, with a maximal normal value at 100). But on liquor there were no auto-antibodies against VOC for K.
Negative result other researches on liquor: Anti AMPA 1 (also on serum), AMPA 2 (also on serum), anti NMDA recepetor (also on serum), anti LGI1 (also on serum), anti GABAb1 (also on serum) and (important datum) anti VOC for potassium (K) on liquor (while, as previously reported, were positive on serum), anti VOC for calcium (also on serum), anti GAD (also on serum) antibodies. And, interesting datum, negative on serum resulted the research of auto-antibodies anti CASPR2, proof that the inflammatory process involving the brain, war related by the auto-antiboides against CAPSR 2 detected only on liquor.
To exclude a paraneoplastic syndrome, the patient performed a PET TAC total body, that gave a negative result.
Finally, a second MRI of the brain, performed after two weeks, demonstrated an inflammatory process prevalent on the right posterior cortex, but also, in minor entity, on the left posterior cortex. Figure 2 is very useful to see the inflammatory process detected by the second MRI of the brain.

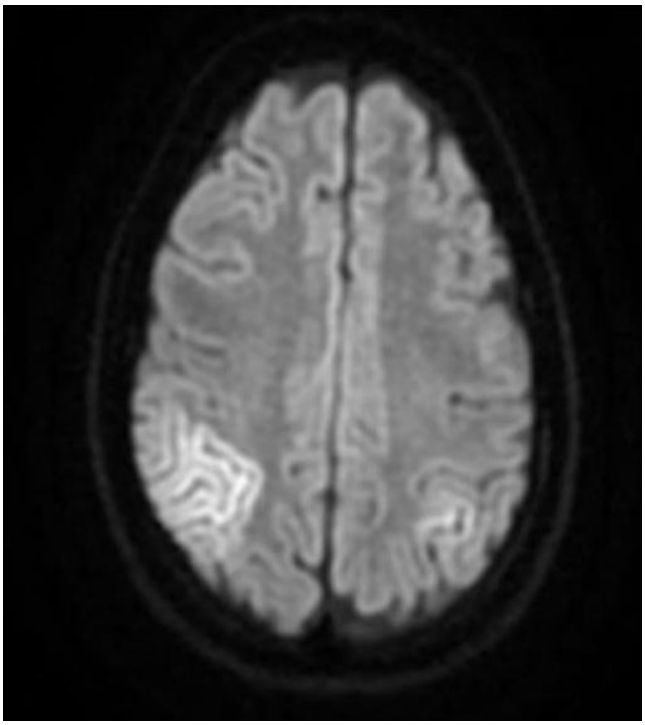

Fig. 2. The second MRI of the brain.

CONCLUSION AND DISCUSSION

This is one example of organic psychosis which would not have replied to psychiatric therapies, because it needed an etiopathogenetic therapy based on a correct diagnosis. This disease regressed only with auto-antibodies chelating therapy, anti CASPR 2, detected both on liquor and on serum.
This case is important also in juridical field, because it demonstrates that psychiatric disorders, often, depend on a disease of the brain, to study when a subject suddenly changes his/her nature.
Unfortunately, to date, there is little attention to this problem.

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