Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Anti-NMDA receptor encephalitis in a psychiatric Covid-19 patient: A case report

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Dear Editor,

Coronavirus disease was first detected in China in December 2019 and contagion has rapidly spread worldwide, becoming a global health emergency. The typical symptoms of COVID-19 can range from mild to severe respiratory illness. In addition to systemic and respiratory symptoms, Human Coronaviruses have been associated with possible pathogenic processes in CNS infection and related neuropsychiatric outcomes (Troyer et al., 2020). The evidence shows that 36.4% of patients with COVID-19 develop neurological symptoms (Wu et al., 2020), Coronavirus infection have been clearly associated with febrile seizures, convulsions, change in mental status and encephalitis (Desforges et al., 2019; Bohmwald et al., 2018).

Italy is one of the countries most affected by the Coronavirus Disease 2019 epidemic. The Lombardy Region, the economic hub of Italy, registered the highest number of positive cases and deaths. At the Niguarda Hospital in Milan, a psychiatric ward was dedicated to COVID-19 positive patients with acute psychiatric disorders (Percudani et al., 2020). From March 9th to April 27th 2020, twenty-four Covid-19 positive patients with acute psychiatric disorders were hospitalized. We report a case of encephalitis associated to immunoreactivity related to SARS-CoV-2 infection in a 23-year-old Ecuadorian male hospitalized for psychotic symptoms characterized by psychomotor agitation, anxiety, thought disorganization, persecutory delusions and auditory hallucinations with commanding voices and global insomnia which appeared over three days. The patient had been suffering from Substance Use Disorder (THC, cocaine and phencyclidine “Angel dust”) since the age of 18 with no medical history of other organic disease reportedly present. Initial laboratory studies included a comprehensive metabolic panel and a complete blood count, both of which were unremarkable (Table 1). Alcohol level was zero and urine drug screen was positive for THC ($>$ 300 ng/mL, normal range $<$ 50 ng/mL). Cerebral CT scan was negative for neuroanatomical acute abnormalities. The patient was initially treated with haloperidol, promazine and intranasal midazolam and subsequently with intramuscolar aripiprazole and oral quetiapine with no clinical response.

The patient showed fever and desaturation (90% saturation in air oxygen). Oxygen therapy was necessary. Chest X-ray revealed bilateral ground glass opacities, Chest CT scan showed patchy bi-basilar consolidations. Confusion, speech and thought disorganization and hallucinatory symptomatology worsened. Antibiotic prophylactic therapy was started, while antipsychotic therapy was discontinued given lack of efficacy and concern for oversedation. Within the second week, the patient was found encephalitic, non-verbal, non responsive to commands: despite being able to move all his extremities and reacting to noxious stimuli. No apparent deficits of Ocular Motility Examination and of cranial nerves was observed. No nuchal rigidity was noted. Neuroradiology did not show significant findings. The EEG showed theta activity at 6 Hz, unstable, non reactive to visual stimuli. No significant asymmetries were seen. The patient started valproate for seizures prophylaxis. The first lumbar puncture did not reveal any evidence of CNS system infection on molecular biology tests, however, biochemical and cellular analysis was not performed for material scarcity. Off-label therapy based on hydroxychloroquine and darunavir/cobicistat was started. Three weeks following hospital admission, the neurological symptomatology worsened, with severe dysphagia, dyskinesias, autonomic instabilities with wide ranging fluctuations in body temperature, blood pressure, respiratory rate and cardiac rhythm. Following deterioration of mental status and increased fever, routine labs and autoimmune panel (Table 1), neuroimaging, CSF examinations were performed with evidence of hyponatremia, increased IL-6 (39 pg/mL, normal range $<$ 7 pg/mL), and CSF anti-NMDA receptor antibodies (Table 2). A diagnosis of anti-NMDAR encephalitis was made. High doses of dexamethasone and intravenous immunoglobulin (IVIG) were administered. Clinical conditions are ameliorating to date.

Anti N-Methyl-D aspartate (NMDA) receptor (anti-NMDAR) encephalitis is one of the most common types of autoimmune encephalitis with its clinical presentation characterized by simultaneous presentation of neurological and psychiatric symptoms, the latter miming schizophrenia and psychotic spectrum disorders or substance induced psychosis (Kayser and Dalmau, 2016). The importance of this case study is due to the probability that COVID-19 leads to neurological damage, an indirect pathway involving the immune system. Interleukin (IL)-6, an important member of the cytokine storm, is positively correlated with the severity of Coronavirus symptoms (Wan et al., 2020). Additional experiments have confirmed that primary glial cells cultured in vitro secrete a large amount of inflammatory factors including IL-6, IL-12, IL-15 and TNF-alpha after being infected with SARS-CoV-2 (Bohmwald et al., 2018). This data suggests that the activation of immune cells in the brain may cause inflammation and brain damage. (Asadi-Pooya and Simani, 2020).

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Table 1
Blood analysis.

	CRP	WBC	N	L	PLT	D-d	ffg	INR	APTT	ALT	AST	ANCA	ANA	Anti-ENA-AB	β2 gp IgG/IgM	CL IgG/IgM	AT	LA screen DRVVt	Tumor Markers**
UM	mg/dL	10^9/L	10^9/L	10^9L	10^9/l	ug/mL	mg/dL	ratio	ratio	U/L	U/L		titre	ratio	U/mL	GPL/ml MPL/ml	%	ratio	
nv	0.0–0.5	4.00–10.00	1.60–7.00	0.80–5.00	140–440	0.00–0.57	180–350	0.86–1.13	0.77–1.23	3–45	0–40	N	N	N	N/N	N/N	83–118	< 1.25	
T0	5.5 *	**10.49** *	6.63	2.86	**83***	**0,72***	**396***	1.13	1.18	**69***	**43***								
T1	**2.5***	**13.83***	9.89	2.37	187			1.13	0.94	**191***	**57***	N	N	N	N/N	**N/56***	**140***	1.19	N

Legend: U.M : unit of measurement; nv: normale values range; T0: time of diagnosis of covid-19 (admission); T1: time of diagnosis of anti-NMDA-R encephalitis; NMDA-R: N-methyl-D-aspartate (NMDA) receptor; CRP: c-reactive protein; WBC: white blood cells; N: neutrophils; L: lymphocytes; PLT: platelet count; D-d: D- dimer; Fg: fibrinogen; INR: international normalized ratio; APTT activated partial thromboplastin time; ALT: alanine transaminase; AST: aspartate transaminase; ANCA: Antineutrophil cytoplasmic antibody; ANA: anti-nuclear-antibody; ENA: extractable nuclear antigens; gp: glycoprotein; CL: cardiolipin; AT: antithrombin; LA: lupus anticoagulant; DRVVt: Diluted Russell Viper Venom Time; AB: antibody; Ig: immunoglobulin; N: negative.

* Alterate value

** Alfa-foetoprotein (AFP): 3.0 ng/mL, range 0.0–7.0 (ECLIA).
Carcinoembryonic antigen (CEA): 3.0 ng/mL, 0.0–5.0 (ECLIA).
Carbohydrate Antigen 125 (CA125): 12 U/mL, 0–35 (ECLIA).
Carbohydrate Antigen 19.9 (CA19.9): 8.1 U/mL, 0.0–37.0 (ECLIA).
Carbohydrate Antigen 15.3 (CA15.3): 7.3 U/mL, 0.0–25.0 (ECLIA).
Neuron-Specific Enolase (NSE): 12 ng/mL, nv < 15.2.
Prostate specific antigen (PSA): 1.25 ng/mL 0.00–4.00 (ECLIA).
Chromogranin: 61 ng/mL 0–108.
Human chorionic gonadotropin. (HCG):absent mUI/mL 0–2 (ECLIA).
Calcitonin: 3.27 pg/mL 0.00–9.52 (ECLIA).

Table 2
CSF analysis: CSF studies show no evidence of CNS infection.

CSF studies	
Appearance	hematic
Red and white blood cells	960 cell/microL
Glucose (normal range 40–70 mg/dL)	70 mg/dL
Proteins (normal range 15–45 mg/dL)	65.4 mg/dL
HSV DNA	negative
EBV, CMV, VZV-DNA	negative
Enterovirus RNA	negative
SARS-CoV-2 RNA	negative
Ab anti Ca++Channel	negative
Ab anti AMPA1,2	negative
Ab anti CASPR 2	negative
Ab anti LGI 1	negative
Ab anti NMDAR	positive

Legend: **HSV** - Herpes 1,2 Simplex Virus, **VZV**: Varicella Zoster Virus; **EBV**: Epstein-bar virus, **CMV** – Cytomegalovirus, PCR- polymerase chain reaction. **AMPA** - alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid, **CASPR** - contactin-associated protein-like 2, LGI1 - antileucine-rich glioma-inactivated 1, NMDA - N-methyl-D-aspartate.

COVID-19 patients having known psychiatric disorders should be monitored closely for neurologic manifestations including headache, dizziness, and symptoms, changes in mental status, meningeal signs, dyskinesias. Patients with severe infection may be at greater risk for developing neurological sequelae and increased mortality. Furthermore, SARS-CoV-2 infection should be considered as a differential diagnosis in psychiatric patients with presentation of sudden onset symptoms including respiratory distress and other Covid-19 related symptoms to avoid wrong or delayed diagnosis.

Authors' contribution

The Authors contributed equally in the preparation and revision of the manuscript

The consent to publication has been obtained by patient.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2020.05.054.

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