



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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Letter to the Editor

May confusion be a misleading initial clinical presentation of COVID-19 in individuals with mood disorders?



ARTICLE INFO

Keywords

Confusion
Delirium
Catatonia
COVID-19
Psychiatry
Depression
Bipolar disorder

Abbreviations

COVID19 CoronaVirus Disease 2019
CSF Cerebrospinal fluid
IgG Immunoglobulin type G
MERS Middle East Respiratory Syndrome
PCR polymerase chain reaction
RNA ribonucleic acid
SARS-COV2 Severe Acute Respiratory Syndrome CoronaVirus 2
SARS Severe Acute Respiratory Syndrome

To the Editor,

During the first month of the COVID-19 pandemic, as psychiatrists, we have observed some misleading initial clinical presentations of COVID-19 in a small series of cases with already known psychiatric disorders. Between March 10th to April 10th, 2020, for all patients admitted in our university-affiliated hospital in Paris-France for a psychiatric reason for admission, the hygiene department recommended to prescribe PCR and viral RNA test in case of evocative clinical manifestations (cough, dyspnea, fever, headache, anosmia...). However, misleading initial presentations were also likely to occur. Indeed, during this period, two males of 54 and 68 years-old, already being diagnosed with mood disorder (one with unipolar, one with bipolar) were diagnosed with COVID-19 while they were presenting only confusion or isolated catatonic symptoms (obnubilation and echolalia). Those symptoms were considered as a change from their previous clinical psychiatric state but were also different from the clinical presentations of their experienced past mood episodes (no previous episodes with confusion nor catatonic symptoms). Fever and respiratory signs occurred only 24 hours later for one of them and never occurred for the second one.

In order to estimate how frequent such a misleading presentation might be observed, we systematically and retrospectively reviewed the medical files of all the patients who were admitted during the same period and diagnosed as SARS-COV2 PCR positive during their stay in our inpatient facilities. We identified five additional patients with

common symptoms of COVID-19. These five patients were diagnosed with mood disorders (3 with bipolar versus 2 with unipolar), with an age range 54- 79 years old and exhibited symptoms of COVID-19 such as fever, respiratory symptoms, cough, myalgia, inflammatory symptoms...) in addition to mood disorders, but without confusion or catatonia. Given this clinical experience, we have estimated that 28% of patients with mood disorders and suffering from the COVID-19 infection display confusion or catatonia as an initial clinical sign. This prevalence is exactly the one found by a systematic review published by [Rogers et al. 2020](#) which identified confusion as a common symptom among patients admitted to hospital for COVID-19, SARS or MERS (27,9% of 129 patients) ([Rogers, et al., 2020](#)), a prevalence estimate obtained from two independent studies. This report concerns mostly in patients with severe forms of the disorder, usually in intensive care units, after several weeks of disease evolution. In those cases, a causality attribution of the confusion to the COVID-19 itself is highly difficult, as it could be caused by hypoxia or many other intensive-care related factors. Confusion was rarely isolated there, and often accompanied by either neurological or psychotic symptoms. Among neurological localization signs, authors describe diffuse corticospinal tract signs with enhanced tendon reflexes, ankle clonus, and bilateral extensor plantar reflexes, or persistent executive function impairment after discharge ([Helms et al., 2020](#)). More recently, 10 cases of confusion and persistent delusional psychotic symptoms were described after several weeks of severe COVID-19 respiratory infection in liaison psychiatry patients ([Parra et al., 2020](#)). Interestingly, cerebro-spinal fluid (CSF) PCR when performed revealed no presence of the virus, ruling out a direct neurotropic deleterious effect of the SARS-COV2. Reversely, some patient from those series showed high protein and IgG levels in the CSF, evocative of a secondary deleterious immune response associated with those neurological signs, as previously reported with MERS and SRAS ([Helms et al., 2020](#)). In this context, little is known whether patients with psychiatric disorders would exhibit confusion or misleading clinical presentation more often than patients with no known psychiatric disorders. Furthermore, our case series was characterized by an age range between 54-74 years old.

<https://doi.org/10.1016/j.psychres.2021.113710>

Received 31 December 2020; Accepted 2 January 2021

Available online 4 January 2021

0165-1781/© 2021 Elsevier B.V. All rights reserved.

It has been reported that confusion or delirium are frequent in elderly patients, including at early stages of the COVID-19 disease, whether recruited in the emergency department or in specific geriatric series (Kennedy et al. 2020; Vrillon et al., 2020). In those series, confusion was present in up to 71% of the subjects and was even the only symptom present in up to 16%. In those elderly patients, a confounding effect of hypoxia or cardiac failure observed in severe COVID-19 forms is still possible. Of note, among the patients recruited in geriatric facilities, 48 (63.2%) had already a diagnosed cognitive impairment (Vrillon et al. 2020), and elderly patients are more vulnerable to confusion or to a worsening of previous cognitive impairment in case of any type of infection (Fard et al., 2020).

Further case series should investigate whether confusion or other misleading presentations such as catatonia might represent frequently the initial clinical presentation of COVID-19.

Since these patients were not initially presenting with severe respiratory signs, we may retain as plausible the hypothesis of confusion or catatonic symptoms linked with an initial non-specific immune response to the virus, similar to fever or fatigue. This is in line with numerous data showing that patients with psychiatric disorders display low grade inflammation, usually accounted for a shared genetic vulnerability. The link between confusion in the early course of a viral infectious disease and this persistent low-grade inflammation needs to be further investigated. Such a study would require a systematic PCR for all patients admitted in psychiatric ward, along with systematic and structured neurological and psychiatric assessment and CSF or at least plasmatic inflammatory and immune response biomarkers, and possibly PET-scan microglial activation measurements.

Pr Florence Vorspan¹, Dr Rishma Amarsy-Guerle², Pr Bruno Etain¹.

1, APHP.NORD, Hôpital Lariboisière-Fernand Widal, Département de Psychiatrie et de Médecine Addictologique

2. APHP.NORD, Hôpital Lariboisière-Fernand Widal, Equipe Opérationnelle d'Hygiène

DECLARATION

Ethics approval and consent to participate

This report follows the French biomedical rules on biomedical research (Loi Jardé) and our hospital policy on the publication of anonymized data collected during routine care. The data repository has a specific authorization from the CNIL (National Commission on Information Technology and Freedom) under the number 2017-013 given on 19 January 2017. Both include the information of the patients and a non-opposition rule.

Availability of data and materials

upon request

Competing interests

All authors report that they do not have competing interest with regards to this work.

Funding

no specific funding for this work.

Authors' contribution

FV wrote the first draft of the manuscript. All authors participated in the discussion and approved the final version of the manuscript.

Acknowledgment

none

References

- Fard, M.T., Cribb, L., Nolidin, K., Savage, K., Wesnes, K., Stough, C., 2020. Is there a relationship between low-grade systemic inflammation and cognition in healthy people aged 60–75 years? *Behavioural Brain Research* 383, 112502. <https://doi.org/10.1016/j.bbr.2020.112502>.
- Helms, J., Kremer, S., Merdji, H., Clere-Jehl, R., Schenck, M., Kummerlen, C., Collange, O., Boulay, C., Fafi-Kremer, S., Ohana, M., Anheim, M., Meziani, F., 2020. Neurologic Features in Severe SARS-CoV-2 Infection. *N Engl J Med* 382, 2268–2270. <https://doi.org/10.1056/NEJMc2008597>.
- Kennedy, M., Helfand, B.K.L., Gou, R.Y., Gartaganis, S.L., Webb, M., Moccia, J.M., Bruursema, S.N., Dokic, B., McCulloch, B., Ring, H., Margolin, J.D., Zhang, E., Anderson, R., Babine, R.L., Hsieh, T., Wong, A.H., Taylor, R.A., Davenport, K., Teresi, B., Fong, T.G., Inouye, S.K., 2020. Delirium in Older Patients With COVID-19 Presenting to the Emergency Department. *JAMA Netw Open* 3, e2029540. <https://doi.org/10.1001/jamanetworkopen.2020.29540>.
- Parra, A., Juanes, A., Losada, C.P., Álvarez-Sesmero, S., Santana, V.D., Martí, I., Urricelqui, J., Rentero, D., 2020. Psychotic symptoms in COVID-19 patients. A retrospective descriptive study. *Psychiatry Res.* 291, 113254 <https://doi.org/10.1016/j.psychres.2020.113254>.
- Rogers, J.P., Chesney, E., Oliver, D., Pollak, T.A., McGuire, P., Fusar-Poli, P., Zandi, M.S., Lewis, G., David, A.S., 2020. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry* 7, 611–627. [https://doi.org/10.1016/S2215-0366\(20\)30203-0](https://doi.org/10.1016/S2215-0366(20)30203-0).
- Vrillon, A., Hourregue, C., Azuar, J., Grosset, L., Boutelier, A., Tan, S., Roger, M., Mourman, V., Mouly, S., Sène, D., François, V., Dumurgier, J., Paquet, C., for LRB COVID Group, 2020. COVID-19 in Older Adults: A Series of 76 Patients Aged 85 Years and Older with COVID-19. *J Am Geriatr Soc.* <https://doi.org/10.1111/jgs.16894>.

Florence Vorspan^{a,b,c,*}, Rishma Amarsy^d, Bruno Etain^{a,b,c}

^a Département de Psychiatrie et de Médecine Addictologique, Hôpital Fernand Widal, APHP.NORD, 75010, Paris, France

^b Université de Paris, Faculté de Médecine, Site Paris Diderot, 75010, Paris

^c INSERM UMRS 1144, Therapeutic Optimization in Neuropsychopharmacology, 75006, Paris

^d EOH, Equipe Opérationnelle d'Hygiène, Hôpital Lariboisière, APHP. NORD, 75010, Paris

* Correspondance to: