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COVID-19-индуцированные психозы: новые вызовы для начинающих карьеру психиатров

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Пандемия COVID-19 и ее влияние на психическое здоровье населения планеты остаются огромными и глобальными во всех смыслах. Ранее сообщалось о различных типах связанных с COVID-19 психических расстройств, включая как новые случаи заболеваний, так и обострение имевшихся ранее, начиная от расстройств адаптации и заканчивая полномасштабными психотическими состояниями.

В данном обзоре рассмотрены различные клинические симптомы индуцированных расстройств, включая систематизированные бредовые идеи, аффективные симптомы и идеи самоповреждения, нуждающиеся в длительном лечении и уходе за пациентами. Были предложены различные этиопатогенетические модели, в т.ч. прямое повреждение нервной системы «цитокиновым штормом» или выявление скрытых уязвимостей, однако эти теории требуют дальнейших исследований. Доказано, что традиционные антипсихотические фармакологические средства работают эффективно в данной ситуации, однако требуется уделять особое внимание потенциальным лекарственным взаимодействиям при сопутствующих заболеваниях и вероятности побочных эффектов.

При подготовке этого обзора мы сотрудничали во Всемирной целевой группой начинающих психиатров и подготовили общую точку зрения на эту проблему.

Ключевые слова: *пандемия COVID-19, психическое здоровье, психотические расстройства, нейробиология, антипсихотики*

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COVID-19-induced psychosis: new challenges for early career psychiatrists

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The COVID-19 pandemic and its impact on mental health has remained immense and global in all senses. Various types of induced psychiatric disorders, both new episodes and exacerbation of the preexisiting ones has been reported - starting from adjustment disorder to full psychotic illnesses.

Various clinical symptoms, including systematized delusions, affective symptoms and self harm ideas has been mentioned needing upto prolonged admission and in patient care. Various etiopathogenetic models, incluing direct neural infection to cytokine storms or unmasking of the hidden vulnerabilities has been proposed however this needs further research. Traditional antipsychotic pharmacological agents has been proven to work well though special attention to pharmacological interactions is needed with caution for co morbid conditions and chance of side effects.

We collaborated in worldwide Task Force of early career psychiatrists and prepared the definition of our point of view.

Keywords: *COVID-19 pandemic, mental health, psychotic disorders, neurobiology, antipsychotics*

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ECO•VECTOR

COVID-19, a global pandemic, started in late 2019, soon got spread all over the world and hit the entire population more than just an infection. Worrisomely yet very importantly, both the burden of mental health problems and already existing morbidities has piled up to an unimaginable level along with global concern for the same. As an obvious, the public health concern of this global mental health scenario has seeked attention to many clinicians and researchers; with variable literature has been published from the entire globe. Both the neurotic as well as psychotic spectrum disorders have been reported and here we discuss the existing literature on COVID-19 related psychosis and psychotic reaction/exacerbations including neurobiology and treatment of the same. In this article, we choose the **aim** — to review the first available data on COVID-19 induced psychoses and the impact of these data on the development of theory and practice. We collaborated in worldwide Task Force of early career psychiatrists and prepared the definition of our point of view.

Neurobiology of COVID-induced psychosis

Establishing a causality relationship in a rare outcome is a challenging task and mandates more extensive experimental research. Historical studies from past viral pandemics and ongoing neurobiological evidence extrapolated from current COVID-19 small studies point towards a causal relationship between SARS-CoV-2 infection and psychosis. However, establishing that new-onset psychosis in previously asymptomatic individuals is either due to the direct neurotrophic effects of the virus or due to unmasking of psychosis in vulnerable individuals, both require further underpinning. The relationship between virus and immune dysregulation in psychosis has been well studied in the past [1] especially during the early utero-development phase. Recently a critical appraisal of reported cases for COVID-induced psychosis postulated several underlying mechanisms for psychosis in COVID-19 patients [2]. Although it is difficult to demarcate whether these alterations in mental state are sequelae of systemic infection, direct neuro-invasion, stress-triggered predisposition in genetically vulnerable, or a combination of all above factors, further research is required. The several potential mechanisms are discussed:

A. Direct neural infection. The key receptor, ACE-2, which is important for SARS-CoV-2 intracellular invasion, is also expressed on neural cells in the brain. Exploratory reports from intranasal inoculation of SARS-CoV-1 infection in ACE2 transgenic mice showed evidence of neuronal loss and upregulation of pro-inflammatory discharge from glial and astrocytes cells in the brain [3]. Micro-invasive potential of SARS-CoV-2 RNA have been reported in CSF of COVID-19 patients [4] and this acute neurotrophic invasion can cause neuropsychiatric symptoms.

B. Cytokine storm and proinflammatory response. One of the more accepted hypotheses that could account for psychosis in COVID-19 patients is 'cytokine storm,' systemic hyper-inflammation which can occur in certain groups of seriously ill patients. There are reports of elevated inflammatory markers in the acute stage of COVID-19, e.g. CRP, serum ferritin, interleukin and an association of these markers with severity of illness [5]. Meta-analyses supporting relevant neurobiological mechanisms linking primary psychotic disorder and cytokine dysregulation have been well studied in the past. Schizophrenia is related to aberrant immune system dysfunction, including cytokine levels [6]. Increased level of a few cytokines might be state markers of the acute phase (IL-6, IL-1β, and TGF- β), while other increased levels of IL-12, IFN-γ and TNF-α may be trait markers of inflammation [5]. Accumulating evidence from COVID-19 studies suggests that the level of proinflammatory cytokines is increased during infection. Further, a subgroup of COVID-19 patients might face cytokine storm [7], which can lead to immune dysregulation and predispose patients to altered mental state.

C. Autoimmunity and iatrogenic. Another potential mechanism that might potentiate the development of neuropsychiatric sequela is molecular mimicry with host self-antigen. CoV infection may mislead the host immune response in susceptible individuals towards autoimmunity and can trigger the cascade of neuronal death in the CNS [8]. Certain medications used for COVID-19 treatment can precipitate a psychotic episode. There is an abundance of reports of corticosteroid-induced psychosis in the past [9]. The potential risk due to high doses of corticosteroid or quinolone use during acute phase SARS CoV-1 infection warrants judicious use of medications.

D. Unmasking hidden vulnerability. COVID-19 is a known psychosocial stressor and this state of heightened stress during a pandemic could trigger the well-established association between stress and psychosis. Increased substance use, isolation, social deprivation, and socio-economic hardship can unmask other relevant causes of psychosis [10].

Clinical manifestations

There have been various reports of people developing psychotic symptoms during the pandemic which were seemingly prompted by the profound and significant distress caused by it [11–14]. These psychotic episodes are often manifested through hallucinations and delusions which tend to be focused on COVID-related themes. For example, Huarcaya-Victoria, Herrera, and Castillo (2020) reported a case of a person listening to a voice which persistently ordered her to be tested for COVID-19. Valdés-Florido and colleagues (2020) also reported a series of four brief reactive psychosis prompted by the distress associated with the ongoing pandemic, with symptoms that included delusions about one's family being infected by the COVID-19 virus, and an extreme worry about being a contagious asymptomatic

carrier and an increased emotional reactivity. Rentero and colleagues (2020) suggested that episodes of psychosis triggered by the pandemic are characterised by a subacute onset of psychotic symptoms and quick recovery on low antipsychotic doses.

Brown et al. (2020) also discusses the effect of covid-19 on psychosis and given an incident rate with a range of 0.9% to 4%. The mentioned association with viral exposure treatment used to manage the infection and potential role of psychosocial stresses behind this.

On the other hand, psychotic episodes associated with COVID-19 infection seem to be characterised by a rapid instauration, and they also appear to resolute with low antipsychotic doses [16-19]. Other symptoms associated with COVID-19 associated psychosis are also hallucinations in various sensory modalities, delusions, and disorganized speech; although disorganized behaviours and confusional features appear to be more prominent in these cases [20,21]. There could also be confusional symptoms, however, these appear to be more related to having received ICU-treatment and the accompanying clinical manifestations of COVID-19 infection [18]. Nevertheless, it should be highlighted that whether there is a direct biological relationship between COVID-19 and psychosis remains unclear [19,22].

Example of affective induced psychosis: A. Correa-Palacio, et al. (2020) reported about a 43 year old gentleman with history of aggressive abusive behavior (both physically and verbally, up to using two swords to fend his arrest) which needed emergency intervention by local police followed by admission at psychiatric in patient unit. Post admission, MSE findings of a hyper alert oriented patient, who was collaborative but with a moderate level of psychomotor restlessness. His speech was loud, re- iterative and logorrheic, with megalomaniac beliefs of «communicating directly with God», and persecutory delusions with medical and police staff. He was expansive and anxious with a high level of self-perceived energy. Visual and auditory hallucinations were recognized by the patient as well as eight-day global insomnia. One mood stabiliser, two antipsychotics and benzodiazepine were needed for his management as well.

Treatment

With regards to psychosis in the context of COVID-19, we find that the treatment, like more traditional forms of psychosis, calls for low dose antipsychotics [18]. Aripiprazole has been noted to be effective in patients who are psychotic either immediately due to an infectious disease or those who are rendered psychotic due to psychosocial stress associated with an infectious disease [15]. For patients who had risk factors for developing psychosis before the pandemic, the literature has recommended being wary of drug induced psychosis (the potential impact) during the COVID-19 pandemic. And finally, for patients with existing psychosis before COVID-19, it has been alluded that clinicians actively advise patients to physically distance and isolate due to the decreased likelihood of patients with psychosis adhering to protective measures [15]. In terms of pharmacotherapy for patients who were treated with clozapine, it was recommended absolute neutrophil count monitoring could be done up to once in three months in certain conditions [24]. In addition, for these same patients, the literature has advised bridging existing technological divide [25] by promoting technological opportunities as this would provide patients with more opportunities with e-health follow up [26]. Ultimately, it is also worth mentioning that patients who are on drugs ought to be monitored for pharmacodynamic and pharmacokinetic interactions between those drugs when it comes to cardiac arrythmia, hematological side effects and effects on the CYP system [15].

CONCLUSION

COVID-19 induced psychosis has piqued the interest of many doctors and researchers, Historical research from previous viral pandemics, as well as ongoing neurobiological evidence inferred from current COVID-19 small studies, suggest that SARS-CoV-2 infection and psychosis are linked. However, determining whether new-onset psychosis in previously asymptomatic people are caused by the virus's direct neurotrophic effects or by the virus's unmasking of psychosis in vulnerable people requires more research. More research is needed to determine if these changes in mental state are the result of systemic infection, direct neuro-invasion, stress-triggered predisposition in genetically predisposed people, or a combination of all the aforementioned variables, and for management of this condition. Also, a mentally health-y public health approach with appropriate policy making and preparedness for emergency mental health services as a part of any similar disaster management needs a serious attention worldwide.

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