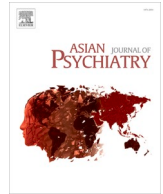




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Short communication

A qualitative analysis of literature reporting and linking psychosis to COVID-19 infection. Findings from a postgraduate journal club

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ABSTRACT

Acute exacerbations of psychosis have been reported with COVID-19 infection and medications used for its treatment. Terms “psychosis”, “psychotic”, “COVID-19” and “coronavirus” were searched on “PubMed” and “GOOGLE SCHOLAR”, yielding 84 articles. 14 case reports were selected based on pre-defined criteria and analyzed. Among selected articles, 10 attributed psychosis to COVID-19 infection. In 3 articles, psychosis was diagnosed despite concurrent delirium. In 8 and 3 articles respectively, a clear temporal demarcation of psychosis and COVID-19 infection and steroid use was not described. Psychosis can occur secondary to GMC, or exposure to medication. Due process should be followed to ascertain the same.

Introduction: Neurotropic coronavirus infection is associated with numerous neurological and neuropsychiatric manifestations. Such presentations before, during and after the infection have been reported. Among these presentations, acute exacerbations of psychosis have been reportedly linked with COVID-19 infection and medications used for its treatment.

Methodology: Search engines “PubMed” AND “GOOGLE SCHOLAR” were searched using specific search terms during June 2021. Out of 84 articles that came up, we selected 14 articles based on pre-determined inclusion and exclusion criteria. Selected articles were analysed and discussed in the departmental journal club.

Results: In 10 articles, diagnosis of psychosis was attributed to COVID-19 infection. In 3 of those articles, despite reporting concurrent delirium like presentation, diagnosis was still reported as psychosis. In 8 articles, the temporal correlation between onset of psychosis, onset of COVID-19 was not clearly demarcated. In 3 articles, clear demarcation between psychosis associated with steroid use and with a general medical condition (COVID-19) was not clearly presented. Only 2 articles did mention using a structured diagnostic system. In patients (3/17) with prior history of psychiatric illness, diagnosis was reported as relapse of psychosis (2/17), without specifying the criteria used for diagnosing a relapse.

Conclusion: Acute exacerbation of psychosis can occur secondary to a general medical condition (GMC), or after exposure to a medication. However, due process should be followed to ascertain that the psychosis is indeed secondary to a GMC, or a medication, and not a de-novo presentation, or delirium.

1. Introduction

Coronaviruses have been linked to neuropsychiatric manifestations during and after the infection (Lahiri and Ardila, 2020; Ellul et al., 2020; Niazkar et al., 2020; Rehman et al., 2021; Rentero et al., 2021; Hyland et al., 2020; Kozloff et al., 2020; Bodnar et al., 2021). Immunological mechanisms, COVID-19 treatment, cognitive impairment, poor psychosocial functioning, pre-existing psychiatric or neurological disorder and adverse geopolitical situations due to the pandemic were hypothesized to be causally associated with presentations of psychosis (Bodnar et al., 2021).

Here we present discussions, deliberations and observations at a departmental journal club, focussing on scientific literature reporting psychosis in patients diagnosed with COVID-19.

2. Methodology

We searched ‘PubMed’ and ‘GOOGLE SCHOLAR’ from June 1st-15th 2021 with keywords “COVID 19”, “CORONAVIRUS”, “PSYCHOSIS”, “PSYCHOTIC”. Fig. 1.

All the articles relevant to the study, as per inclusion and exclusion criteria, were taken up and analysed. Concerns with regards to reporting

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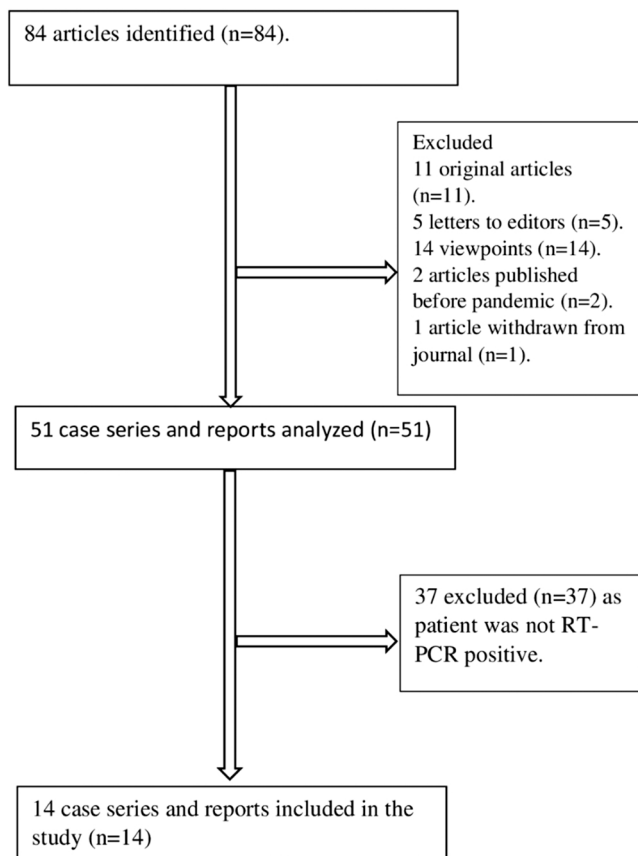


Fig. 1. Procedure of data extraction.

psychosis in COVID-19 pandemic were highlighted.

3. Results and discussion

We used the guidelines and criteria mentioned in DSM-5 (American Psychiatric Association et al., 2013) for psychotic disorders due to other medical conditions, and judged (Supplementary Table 1) whether there exist with psychosis;

1. A temporal relationship after COVID-19 infection.
2. Symptoms that are atypical in nature and course.
3. A possible link with a medication/substance of abuse.
4. a pathophysiological relationship with COVID-19 infection.

In most articles the title hinted at a link between psychosis and COVID 19 (Hansen et al., 2020; Parker et al., 2021; Alba et al., 2021; Noone et al., 2020; Kozato et al., 2021; Smith et al., 2020; Lim et al., 2020; Lanier et al., 2020; Majadas et al., 2020; Correa-Palacio et al., 2020). Two articles suggested a possible role of quarantine in onset of psychosis (Sanchez et al., 2020; Baral et al., 2021). Psychosis was reported in some articles as the presenting feature of COVID-19, (Parker et al., 2021; Noone et al., 2020; Lanier et al., 2020; Correa et al., 2020; Ferrando et al., 2020; Saje et al., 2021), whereas, some reported psychosis as a neuropsychiatric manifestation following symptoms of COVID-19 (Hansen et al., 2020; Alba et al., 2021; Noone et al., 2020; Kozato et al., 2021; Smith et al., 2020; Lim et al., 2020; Majadas et al., 2020; Baral et al., 2020).

3.1. Observation 1: establishment of temporal association

To diagnose psychosis due to a general medical condition, a temporal association between the two has to be established. We found articles that

mentioned psychosis as the presenting feature of COVID-19 (Parker et al., 2021; Noone et al., 2020b; Lanier et al., 2020; Correa-Placio et al., 2020; Ferrando et al.; Saje et al., 2021).

Eight (Hansen et al., 2020; Alba et al., 2021; Noone et al., 2020a; Kozato et al., 2021; Smith et al., 2020; Lim et al., 2020; Majadas et al., 2020; Baral et al., 2021) have reported COVID-19 like illness prior to onset of psychotic symptoms. Eight have not shared the details regarding duration passed between a positive RT PCR swab and onset of psychosis (Sanchez et al., 2020; Parker et al., 2021; Kozato et al., 2021; Lanier et al., 2020; Majadas et al., 2020; Correa- et al. 2020; Ferrando et al., 2020; Saje et al., 2021).

The stressors in workplace/life and infections, metabolic imbalances, chronic debilitating diseases act as psychological stressors and hence precipitate psychosis (Phillips et al., 2007; Corcoran et al., 2003). Loss of livelihood, separation from loved ones during mandated quarantine can trigger psychosis in vulnerable individuals (Martin et al., 2021). Also, hallucinations, delusions might predispose patients to disregard COVID-19 safety protocols (American Psychiatric Association et al., 2013; Valdés-Flórido et al., 2020). Thus, it is questionable what came first, the infection or the psychosis, while reporting such clinical phenomena.

3.2. Observation 2: presence/absence of atypical symptoms

Atypical symptoms such as, hallucinations (other than auditory) and delusions with themes like somatic, grandiose, religious and persecutory (American Psychiatric Association et al., 2013), points towards diagnosis of psychosis due to another medical condition. Most articles have reported this specific symptom profile except two (Alba et al., 2021; Lanier et al., 2020).

Atypical age at onset, is one of the guidelines for considering psychosis due to another medical condition (American Psychiatric Association et al., 2013). In this study, mean age at onset of psychotic episodes was above 40 years, which is within the second of the bimodal peaks of schizophrenia onset (Sham et al., 1994). Psychotic disorders show a marked prevalence between 15 and 17 years (American Psychiatric Association et al., 2013; Kessler et al., 2007, World Health Organization et al., 2004), higher age at onset can be atypical for onset of psychosis.

3.2.1. Observation 3: presence of psychosis due to general medical condition, or Substance/Medication Induced Psychotic Disorder

Use of steroids is a mainstay of treatment in severe COVID-19. (Mølhave et al., 2021). It is known to cause psychosis (American Psychiatric Association et al., 2013), which manifest within one to two weeks of initiation (Kenna et al., 2011). Three articles mentioned the use of steroids in treatment of COVID-19, without mentioning dose, and duration of time between initiation of steroids and onset of COVID-19 (Kozato et al., 2021; Majadas et al., 2021; Correa et al., 2020).

Incidence of psychiatric symptoms with steroid use averages to about 28% (Lewis et al., 1983). Increasing doses of prednisone (> 40 mg) and dexamethasone (>15 mg) are associated with increased psychosis (Lewis et al., 1983; Janes et al., 2019). Overall, psychiatric manifestations can occur early in the course of treatment or even after cessation of the drug (Lewis et al., 1983). Various routes of administration have shown variable incidences of psychosis, with parenteral routes showing the most (Janes et al., 2019; Upadhyaya and James, 2019).

Antivirals are also reported to cause psychosis (Caubet et al., 2011).

Hence, while reporting psychosis due to another medical condition, background treatment modalities and their side effect profiles should be considered.

3.3. Observation 4: establishment of pathophysiological relation- Inflammatory markers

Patients with COVID-19 have raised inflammatory markers such as D-dimer, CRP, BUN, IL-6 (Parker et al., 2021, ICMR COVID 19 National

Task Force). Five articles did not give details about inflammatory markers (Hansen et al., 2020; Sanchez et al., 2020; Alba et al., 2021; Correa-Palacio et al., 2020; Saje et al., 2021), while in others, inflammatory markers were within normal limits (Noone et al., 2020; Kozato et al., 2021; Smith et al., 2021; Lim et al., 2021). Among inflammatory markers, CRP was most often raised (Majadas et al., 2020; Ferrando et al., 2020; Baral et al., 2021) followed by BUN (Parker et al., 2021).

Inflammatory markers such as IL-1 beta, IL-6 and growth factors like GF beta can be raised during acute exacerbations in schizophrenia (Kirkpatrick et al., 2013). Stress due to infections or metabolic instability can also raise inflammatory markers and cytokines (Marsland et al., 2017). Further, remission of psychosis is accompanied by reduction in level of inflammatory markers (Haring et al., 2015). Fluvoxamine, an antidepressant gained a brief spotlight during the pandemic and it was hypothesized that fluvoxamine, due to its activation of S1R-IRE1 pathway, reduced the inflammatory markers, thus alleviating symptoms of COVID-19 (Lenze et al., 2020). It may therefore be prudent to consider that, inflammatory markers, though elevated in acute infections, can also be elevated in psychiatric disorders themselves.

3.4. Observation 5: diagnosis attributed to delirium or psychosis?

Three reports stated that patients had signs and symptoms of delirium in concurrence with psychosis (Noone et al., 2020a; Lim et al., 2020; Majadas et al., 2020), yet all 3 reported the diagnosis as psychosis. In one, a patient admitted in an ICU reported behavioural symptoms, with fluctuating orientation, yet the diagnosis reported was psychosis (Kozato et al., 2021).

The criteria for diagnosing delirium include disturbance of awareness, change in baseline cognition and a fluctuating course (American Psychiatric Association et al., 2013). Despite the occurrence of delusions and hallucinations in both delirium and psychosis, the differentiating feature is the background of clear consciousness in psychosis. (American Psychiatric Association et al., 2013, World Health Organization et al., 2004). COVID-19 patients admitted in isolation or in the ICU can experience sensory deprivation. This, along with multitudes of medications used in treatment and their interactions may predispose patients to delirium or more often sub-syndromal delirium, which can be overlooked or missed (Sepulveda et al., 2017). Thus, there is a possibility of delirium masking or masquerading as psychosis in COVID-19 infection.

3.5. Observation 6: miscellaneous

One article reported case of an adult male with pre-existing schizoaffective disorder, on a maintenance dose of clozapine, who presented with psychosis during mandated quarantine after a febrile illness (Sanchez et al., 2020). It was reported as a relapse of psychosis. However, schizoaffective disorder require coexistence of either depressive or manic episode with core symptoms of schizophrenia for at least a month (American Psychiatric Association et al., 2013), which was not fulfilled in the clinical presentation described. In the same report, details about whether clozapine was discontinued, or down-titrated during the febrile illness were not mentioned. This history is relevant, since high grade fever (101 F) in a patient taking clozapine warrants investigations to rule out agranulocytosis, or Neuroleptic Malignant Syndrome (NMS) (Karagianis et al., 1999). These can mimic symptoms of COVID-19 and the following psychotic episode could have been due to, reduction/discontinuation of clozapine, or physical/psychological burden of febrile illness.

In some articles, chronic and severe metabolic, infectious and degenerative disorders were reported during the clinical work-up, such as hepatic encephalopathy, Lewy Body Dementia and Toxoplasmosis (Parker et al., 2021). All these can present with behavioural disturbances or delirium caused by the disease process, yet, the diagnosis was reported as psychosis due to COVID-19.

There is handful literature that explained these issues previously

(Dinakaran et al., 2020; Megahed et al., 2020; Ashrafi et al., 2020; Banerjee et al., 2020). This article highlights important concerns about reporting a clinical phenomenon occurring concurrently with another comorbid illness. This is perhaps the first such effort in this domain. It is vital for scientific writers not to engage in the age old fallacy; Event X happened after Event Y; therefore, Event Y must have caused Event X!

In any review of a scientific database, first thing one gets to see are the titles of manuscripts (Dewan and Gupta, 2016; Chapnick et al., 2019; Andrade et al., 2011), and then the abstracts. Hence, it is important that they reflect what the manuscript reports in detail. Heightened emotions and fear among masses are a part and parcel of any pandemic, especially when the causative factor is unknown and thus, over-representation and hype from misleading titles can deviate research from their imperative goal (Boutron et al., 2018).

This manuscript also has some limitations. Due to heterogeneity in design, we limited our research only to case reports and series and excluded randomised trials and observational studies. Since our search was conducted in the month of June 2021, articles published on later dates might have employed a more exploratory and indirect approach in reporting this clinical phenomenon.

4. Conclusion

Patients with COVID-19 can present with psychosis or other psychiatric symptoms at any stage of the infection. However, it is important to differentiate the presentations as, (1) de novo presentation of psychosis, (2) psychosis due to psychological or physiological burden of COVID-19, (3) psychosis due to various geopolitical changes associated with the pandemic, (4) psychosis as a consequence of various medications used in treatment of COVID-19 and (5) delirium.

All ethical guidelines were followed thoroughly during this research and respective authors for each article were cited appropriately.

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Conflict of interest

There is no conflict of interest from any authors.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ajp.2022.103099](https://doi.org/10.1016/j.ajp.2022.103099).

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