Aggressive Behavior in a Critically Ill COVID-19 Patient: Possible Role of Medication Discrepancies

Negar Javidmehr[1], Vahid Reisi-Vanani[1], Mina Borran[2*]

[1]Student Research Committee, Shahrekord University of Medical Sciences, Shahrekord, Iran.
[2]Department of Internal Medicine, School of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran.

Received: 2022-11-01, Revised: 2022-12-25, Accepted: 2023-01-06, Published: 2023-03-31

Abstract

Coronavirus disease 2019 (COVID-19) has different clinical manifestations that besides its iatrogenic intervention could affect brain cognitive function. Medication omission has serious effects on a patient's clinical course changing the disease's mortality and morbidity; herein possible role of the iatrogenic intervention that increased the risk of psychological disturbance including medication omission was reported.

A 40-years-old man with a history of gout treated with allopurinol was admitted due to productive cough and hemoptysis. His physical exam and lung spiral chest CT scan revealed moderate to severe lung infiltrations in favor of COVID-19 which was confirmed with COVID-19 RT-PCR. Due to his clinical course tocilizumab, methylprednisolone pulse, and other conservative therapies were started while allopurinol was omitted. During his hospitalization anxiety and irritability appeared and progressed gradually making him refuse to get oxygen supplementation. Through immediate intervention and controlling his behavioral symptoms with psychotherapy, selective serotonin reuptake inhibitors, benzodiazepines, and initiation of allopurinol, the patient's psychological disturbance were relieved. In the end, he died due to acute respiratory distress syndrome.

COVID-19 and its iatrogenic interventions could trigger a psychiatric disturbance in patients with a variety of pathways. Corticosteroid therapy, non-hypnotic antihistamines, quarantine stress conditions, hypoxia, and medication omission are underlying factors for it. Reporting this medication omission would help physicians become familiar with this pharmacological phenomenon, its prevention, and the way to respond to it. On the other hand, researchers can study the etiology of this phenomenon to understand the mood-stabilizing role of allopurinol in additional studies.

J Pharm Care 2023; 11(1): 54-57.

Keywords: Medication Discrepancies; Medication Reconciliation; COVID-19; Adverse Drug Events

Introduction

Psychiatric consequences of Coronavirus disease (COVID-19) caused by the SARS-CoV-2 are well-defined. COVID-19 can exacerbate pre-existing psychological disorders (1). Cytokine storm, immune responses, hypoxia, and hypoperfusion of the frontotemporal lobe can justify COVID-19 psychiatric manifestations (1-3). Critical illness during COVID-19 is a significant risk factor for psychiatric consequences (3,4). On the other hand, a history of psychological conditions, especially mood disorders, is a predisposing factor for severe COVID-19, hospitalization, and mortality (5). Further, some iatrogenic interventions, including covid-19 pharmacotherapy and medication discrepancies during COVID-19 treatment, can exacerbate the mental condition, besides COVID-19 progression (6-8). Medication discrepancies can lead to serious adverse drug events (ADE) and deteriorate patient outcomes during the pandemic (9). Here, we discuss the possible role of medication discrepancies, the lack of medication reconciliation services, and subsequent ADEs in patient outcomes during Covid-19 hospitalization.

Case presentation

A 40-years-old gentleman was admitted to the emergency department of our hospital due to a productive cough and hemoptysis, which started five days ago. His nasopharyngeal sample's reverse transcription polymerase chain reaction (RT-PCR) was positive for the SARS-CoV-2 virus. He had been refused COVID-19 vaccination. His body mass index was 32.4 kg/m2, and

Corresponding Author: Dr Mina Borran
Address: Department of Internal Medicine, School of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran.
Email: borran.m@skums.ac.ir

his medical history was positive for dyslipidemia and gout for three years, managed by atorvastatin 20 mg /day and colchicine 1 mg/day and allopurinol 300 mg/day since then. A physical exam on admission revealed tachypnea with an O2 saturation of 87% on ambient air and stable other vital signs. Crackles in the base of both lungs accompanied by rhonchi were also recorded. Lung High-resolution computed tomography (HRCT) revealed severe infiltration of both lungs with crazy paving and ground glass opacities. Following Covid-19 definite diagnosis on the first day of admission, the pharmacotherapeutic plan was as follows: dexamethasone (24 mg/day), remdesivir 200 mg/day, enoxaparin 40 mg/day, bromhexine 16 mg/day, montelukast 10 mg/day, pantoprazole 40 mg/day. Medication reconciliation had not been conducted then; consequently, atorvastatin, colchicine, and allopurinol did not continue, and medication history was ignored. The second dose of remdesivir 100 mg/day and the first dose of tocilizumab 800 mg/day were administered the next day. On the third day of hospitalization, the patient received the second dose of tocilizumab without any other changes in the pharmacotherapy regimen. On the fourth day, he commenced anxiety, anger, and agitation; consequently, chlordiazepoxide (10 mg/day) was started as a symptom control agent. Along with psychiatric manifestation, the course of the illness was exacerbated, and respiratory distress and severe hypoxia occurred. The patient underwent non-invasive ventilation, and methylprednisolone sodium succinate 250 mg/day was substituted for dexamethasone. Due to his psychological disturbance, a psychiatry consultation was requested that recommended oral olanzapine 2.5 mg/day, although the patient was aggressive and refrained psychiatry visit. On seven days of hospitalization, progressive hypoxia resulted in translocation to the intensive care unit (ICU) and intubation. Cardiac arrhythmia, i.e., atrial fibrillation with a rapid ventricular response (RVR) and cardiogenic shock, also occurred during ICU admission. Unfortunately, the patient passed away on the twelfth day of hospitalization due to cardiac arrest in the context of acute respiratory distress syndrome.

The patient had no documented psychiatric history and denied any psychopharmacologic agent administration. However, family consultation revealed episodes of insomnia, anxiety, and aggression leading to a street brawl and being arrested by police, raising the possibility of undefined psychiatric disorders history. The patient's wife emphasized that this kind of aggression did not occur during the past 2-3 years when the patient was on gout medication (300 mg/day allopurinol) but relapsed during hospitalization. This scenario triggered us to discover a possible ADE in the patient's course of illness. Therefore, we tried to cover the pros and cons of the patient's pharmacotherapeutic plan.

Discussion

Allopurinol is a urate-lowering agent via xanthine oxidase inhibition and the prevention of degradation of purine metabolites. Allopurinol is approved to manage gout, hyperuricosuria nephrolithiasis, and hyperuricemia in tumor lysis syndrome. Besides urate-associated indications of allopurinol, there are some psychiatric effects (10). Studies have shown that allopurinol inhibits purine production and, due to its secondary metabolites, including adenosine, guanosine, and inosine, can affect dopamine receptors, D2, and reduce dopaminergic activity by a mechanism similar to sodium valproate and lithium as a mood stabilizer (11, 12). Moreover, allopurinol was an effective treatment of refractory aggression in two case series of eight patients (12, 13). Our patient case experience an aggression relapse following allopurinol discontinuation during covid-19.

In addition to allopurinol, atorvastatin and colchicine were discontinued and underwent omission error in the presented case. Slower progression of COVID-19 among ICU admitted patients on atorvastatin is reported (14). Moreover, discontinuation of atorvastatin during hospitalization is associated with increased mortality risk among this group of patients (15). Our patient was also on atorvastatin 20 mg/day, which was discontinued at the time of admission. Improvement of moderate to severe covid-19 outcomes with colchicine administration is concluded by a systematic review and meta-analysis of 5778 COVID-19 patients' data (16). Colchicine omission can also be a risk factor for his COVID-19 progression. Although these ADEs cannot be assumed as the main reason, their role in disease exacerbation cannot be disclaimed.

Unintentional medication discrepancies during hospital admission can lead to significant consequences and increase morbidity and mortality. The omission errors are among the most frequent ones (17). Incidence and risks of these errors vary in different centers, but unintentional ignorance, patients' refusal, inability to take medicine, and unavailability of drugs in hospitals are the most common reasons for omission errors. There are several strategies to diminish these errors, like increasing staff knowledge of medication errors and the way to prevent them. Medication reconciliation is a proven method to minimize unintentional medication discrepancies and ADEs. (18-20). This patient underwent three omission errors which might influence his disease progression and aggression relapse episode.

Montelukast is a leukotriene receptor antagonist that showed some outcome improvement in addition to symptom control in the covid19 patients (21). Montelukast 10 mg daily was started on our patient's first hospitalization day. Montelukast is a generally well-tolerated agent; however, post-marketing studies reported neuropsychiatric ADEs. A cohort study showed an association between montelukast administration and aggressiveness, insomnia, and irritability, especially within two weeks of administration (7, 21). In March 2020, the United States food and drug administration added a black box warning to the montelukast label to emphasize the neuropsychiatric ADEs. Montelukast initiation might have a role in the aggression of the mentioned patient case, besides other possible reasoning. Corticosteroids

can also cause psychiatric disorders, including emotional and behavioral presentations. The most critical risk factor is the dosage. Prednisolone 80mg/day is more likely to have a psychiatric reaction than 40mg/day. The onset of corticosteroid-induced psychiatric disorders is a few days after the first dose. Antipsychotic and mood stabilizing drugs might be needed (6, 8). This patient was on high-dose corticosteroids, either dexamethasone or methylprednisolone, which can affect the course of psychiatric presentations. We did not find a meaningful relationship between other medications administered during hospitalization and neuropsychiatric disturbances.

In conclusion, COIVD-19 can influence mental health and exacerbate underlying psychiatric disturbances in a bidirectional relationship. Although the mentioned patient had several risk factors for severe COIVD-19, including an unvaccinated state, obesity, and possible underlying psychiatric condition, the role of ADEs cannot be ignored. As ADEs are modifiable, clinicians should strive to minimize them in every health care setting. Finally, we implemented medication reconciliation as a routine screening by a clinical pharmacist in our hospital to prevent serious drug discrepancies.

Conflict of Interest

The authors report no conflicts of interest.

References

1. Stamu-O'Brien C, Carniciu S, Halvorsen E, Jafferany M. Psychological aspects of COVID-19. J Cosmet Dermatol. 2020;19(9):2169-73.
2. Wenting A, Gruters A, van Os Y, et al. COVID-19 neurological manifestations and underlying mechanisms: a scoping review. Front Psychiatry. 2020;11:860.
3. Steardo L, Verkhratsky A. Psychiatric face of COVID-19. Transl Psychiatry. 2020;10(1):1-12.
4. Mazza MG, De Lorenzo R, Conte C, et al. Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. Brain Behav Immun. 2020;89:594-600.
5. Castro VM, Gunning FM, McCoy TH, Perlis RH. Mood disorders and outcomes of COVID-19 hospitalizations. Am J Psychiatry. 2021;178(6):541-7.
6. Staub Y, Suga Y, Ikawa Y, et al. Detailed assessment and risk factor analysis of corticosteroid-induced psychiatric disorders in pediatric, adolescent, and young adult patients undergoing induction or consolidation therapy for hematologic malignancy. J Oncol Pharm Pract. 2020;26(5):1041-51.
7. Benard B, Bastien V, Vinet B, Yang R, Krajinovic M, Ducharme FM. Neuropsychiatric adverse drug reactions in children initiated on montelukast in real-life practice. Eur Respir J. 2017;50(2).
8. Thibaut F. Corticosteroid-induced psychiatric disorders: genetic studies are needed. Springer; 2019. p. 623-5.
9. Elbeddini A, Almasalkhi S, Prabaharan T, et al. Avoiding a Med-Wreck: a structured medication reconciliation framework and standardized auditing tool utilized to optimize patient safety and reallocate hospital resources. J Pharm Policy Pract. 2021;14(1):1-10.
10. Bartoli F, Crocamo C, Clerici M, Carra GJTBJoP. Allopurinol as add-on treatment for mania symptoms in bipolar disorder: systematic review and meta-analysis of randomised controlled trials. Br J Psychiatry. 2017;210(1):10-5.
11. Carr CN, Straley CM, Baugh TB. Allopurinol for the treatment of refractory aggression: a case series. Pharmacotherapy. 2017;37(6):748-54.
12. Chen AT, Malmstrom T, Nasrallah HA. Allopurinol augmentation in acute mania: a meta-analysis of placebo-controlled trials. J Affect Disord. 2018;226:245-50.
13. Lara DR, Belmonte-de-Abreu P, Souza DO. Allopurinol for refractory aggression and self-inflicted behaviour. J Psychopharmacol. 2000;14(1):81-3.
14. Rodriguez-Nava G, Trelles-Garcia DP, Yanez-Bello MA, Chung CW, Trelles-Garcia VP, Friedman HJJCC. Atorvastatin associated with decreased hazard for death in COVID-19 patients admitted to an ICU: a retrospective cohort study. Crit Care. 2020;24(1):1-2.
15. Andrews L, Goldin L, Shen Y, et al. Discontinuation of atorvastatin use in hospital is associated with increased risk of mortality in COVID-19 patients. J Hosp Med. 2022;17(3):169-75.
16. Hariyanto TI, Halim DA, Jodhinata C, et al. Colchicine treatment can improve outcomes of coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. Clin Exp Pharmacol Physiol. 2021;48(6):823-30.
17. Masse M, Yelnik C, Labreuche J, et al. Risk factors associated with unintentional medication discrepancies at admission in an internal medicine department. 2021;16(8):2213-20.
18. Lester PE, Sahansra S, Shen M, Becker M, Islam S. Medication reconciliation: An educational module. MedEdPORTAL. 2019;15:10852.
19. Shandilya S, Nizamuddin K, Faisal MW, Noor S, Abraham S. Omitted medications: a continuing problem. Clin Med. 2015;15(1):12.
20. Li XJ, Moola S. Strategies to reduce medication omissions in an acute medical unit of an acute tertiary

hospital: a best practice implementation project. JBI Evidence Synthesis. 2016;14(6):347-61.

21. Khan AR, Misdary C, Yegya-Raman N, et al. Montelukast in hospitalized patients diagnosed with COVID-19. J Asthma. 2022;59(4):780-6.

PLEASE CITE THIS PAPER AS:

Javidmehr N, Reisi-Vanani V, Borran M. Aggressive Behavior in a Critically Ill COVID-19 Patient: Possible Role of Medication Discrepancies. J Pharm Care 2023; 11(1): 54-57.