Bipolar I Disorder Exacerbation Following COVID-19 Vaccination

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ABSTRACT

We present the cases of a 60-year-old female patient and 40-year-old male patient who experienced exacerbations of previously well-controlled symptoms of bipolar I disorder (BD1) after receiving COVID-19 vaccines, despite being stable for years on the same medications. The first patient experienced worsened depression, mania, and psychosis that improved with an increase in risperidone. The second patient experienced depression, mania, psychosis, and suicidal ideation that resulted in hospitalization. Prior to hospitalization, he took lamotrigine and bupropion, the latter of which was changed to aripiprazole in hospital. We reviewed current literature on inflammation in mental disorders, vaccination-related inflammatory changes, and the type of inflammation induced by COVID-19 vaccines. Inflammation is a component of psychiatric disorders, and the inflammatory response induced by vaccines might potentiate acute mental health exacerbations, necessitating treatment changes. However, this case series should not be used to justify recommendations against vaccination without larger, well-designed studies. At this time, the known benefits of vaccination outweigh these unknown risks, especially because individuals with serious mental illness are more likely to die from COVID-19 than the general population.

KEYWORDS: Inflammation, vaccine, COVID-19, depression, mania, psychosis, bipolar

A promising development in the study of psychopathophysiology has been the emergence of evidence that inflammation and its chemical mediators play a role in the development and exacerbation of depressive, bipolar, and psychotic disorders.[1–11] Inflammatory markers, such as interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), are seen in acutely ill patients with these three disorder classes.[1–11] Additionally, individuals with worsening schizophrenia have elevated levels of interferon-gamma (IFN-γ),[1,4,11] and those with depression have increased cluster of differentiation (CD)4/CD8 and T helper type (Th)1/Th2 ratios.[3] Such findings have prompted investigation into the relationship between situations that increase inflammation and neuropsychiatric exacerbations.

One common vector of inflammation is vaccination. The presentation of antigens, either directly or via messenger ribonucleic acid (mRNA), creates a pro-inflammatory state to generate a desired immune response. For example, studies have shown elevated pro-inflammatory markers, such as IL-6 following influenza vaccination[12] and IL-6 and IFN-γ, following bacille Calmette-Guerin (BCG) vaccination in mice and humans, respectively.[13] In the case of COVID-19, the mRNA vaccine for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) elicits a Th1-biased immune response in mice, humans, and macaques, with an increase in IFN- γ, TNF, and CD4 and CD8 T cells.[14–17]

Here, we present two cases of previously stable individuals with acute worsening of their bipolar I disorder (BD1) symptoms after receiving the COVID-19 vaccine, prompting hospitalization for one patient and changes in medication for both. To our knowledge, this is the first case report of this type. We then review current literature discussing the relationship between inflammation and psychiatric illness, along with the role of vaccination in inducing acute exacerbations, to increase awareness of potential complications for better management of mental disorders.

CASE 1

A 60-year-old African American female patient with previously stable BD1 presented to the office after three weeks of depressed mood, anxiety, and decreased need for sleep. She was observed to have increased energy, impulsivity, labile affect, verbose speech with repetitive phrases, tangential thinking and flight of ideas, paranoia, and ideas of reference, consistent with a mixed episode with psychotic features. She reported that her symptoms began within a week of receiving the second dose of the Pfizer-BioNTech COVID-19 vaccine. She denied suicidal and homicidal ideations. Her symptoms were distressing and led her to call off work repeatedly, despite satisfaction with her job. She had a Patient Health Questionnaire-9 (PHQ-9) score of 5. Her prescription of risperidone 2mg, which on she had been stable for eight years, was temporarily increased to 3mg, and

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her symptoms returned to baseline after two weeks.

The patient was diagnosed with BD1 when she was 35 years old, after voluntary hospitalization for depression, mania, and paranoia. Thirteen years prior to vaccination, she had an exacerbation of symptoms due to medication nonadherence, leading to hospitalization, after which she was stable on both mirtazapine 15mg and risperidone 2mg daily until after her COVID-19 vaccination. Of note, she was previously assessed 17 days before vaccination, when she had no active symptoms and a PHQ-9 score of 0.

CASE II

A 40-year-old White male patient with previously stable BD1 and attention deficit hyperactivity disorder (ADHD) was voluntarily hospitalized due to a mixed episode with psychotic features. He reported depressed mood, suicidal ideation, and auditory hallucinations encouraging him to kill himself, but denied homicidal ideation. Upon admission, he was observed to have hyperactivity, impulsivity, irritability, flight of ideas, labile affect, pressured and hyperverbal speech, tangential thought processes, limited attention, and poor short- and long-term memory, with limited recall of three objects after five minutes and major historical events. He reported that his symptoms began after receiving the second dose of the Moderna COVID-19 vaccine and subsequently worsened after he discontinued his medications five days prior to admission. He lost his job after a verbal altercation with his boss, prompting him to seek inpatient treatment. His symptoms stabilized after 10 days with aripiprazole 15mg every morning, lamotrigine 25mg twice a day, and quetiapine 100mg every night while inpatient, and was discharged with aripiprazole 15mg every morning and lamotrigine 100mg daily.

The patient was diagnosed with BD1 and ADHD when he was 16 years of age. He received consistent psychiatric services starting at the age of 25 years. His only previous hospitalization was five years prior to vaccination for mania and impulsivity, after which his symptoms were stable with bupropion 50mg daily and lamotrigine 100mg daily, prior to receiving the COVID-19 vaccination. Drug screens throughout his treatment were negative.

DISCUSSION

We presented two cases of individuals with BD1 who developed acute exacerbations after receiving a COVID-19 vaccine. Our 60-year-old female patient had been stable for 13 years and required increased risperidone to return to baseline. Our 40-year-old male patient had been stable for five years and required hospitalization and the addition of aripiprazole with his lamotrigine.

As previously mentioned, there is a relationship between elevations in inflammatory mediators and exacerbations of psychiatric illness. Individuals with BD1 experiencing acute depression and mania have been found to have a concomitant rise in IL-6, CRP, and TNF-α with mania, exhibiting a greater increase in CRP than individuals with depression.[1,6,7,9] Additionally, depression in those with major depressive disorder (MDD) is associated with increases in Th17 cells, CD4 cells, and the Th1/Th2 ratio.[2,3] The polarization of T helper cells toward the Th1 response would increase levels of IL-2 and IFN-γ.[18] Of note, the maximum level of pro-inflammatory mediators correlates with depression severity but has yet to be tied to severity of manic episodes.[3,9] However, elevated inflammatory markers have been linked with acute mania when compared to six-month follow-up.[8] Similarly, in studies of schizophrenia, IL-6, TNF-α, IFN-γ, and transforming growth factor (TGF)-β have been found to be elevated in acutely relapsed patients.[4,10]

The aforementioned pro-inflammatory markers have been linked with acute depression, mania, and psychosis, without known triggering events to increase these levels. It is theoretically possible that if an individual were to experience a pro-inflammatory insult, such as a vaccine, these inflammatory mediators might increase and precipitate psychiatric decline. While there are no definitive studies to show that vaccines can lead to inflammation, which can, in turn, lead to psychiatric problems, there are studies of psychiatric status postvaccination that demonstrate a correlation. Two such studies showed increased symptoms of depression after the influenza and BCG vaccines in humans and mice, respectively. Following administration of the influenza vaccine, college students exhibited elevated IL-6 levels and depressed mood. The magnitude of change of IL-6 varied between individuals, and the degree of which levels increased directly correlated with greater increases in depressed mood.[12] In mice who had received the BCG vaccine, there were notable increases in IL-6 and IFN-γ that were associated with the depression-like behavior of decreased activity during activity testing.[13]

Some of the above markers, along with others, that are present in psychosis, depression, and mania are either proposed or proven to be elevated following COVID-19 mRNA vaccination. The Pfizer-BioNTech vaccine has led to Th1 polarization of the T helper cell response, typical of mRNA vaccines, with increases in IFN-γ, IL-2, and TNF.[14,18] A study with a vaccine comparable to Pfizer-BioNTech and Moderna showed similar results in mice.[16] The Moderna vaccine in humans creates a Th1 directed CD4 T cell response, with prevalence of TNF-α and increased magnitude of IL-2 and INF-γ.[15] The Curevac vaccine in macaques in Germany has led to elevated IFN-γ, peaking two weeks postvaccination.[17] A computerized model of a mRNA vaccine against SARS-CoV-2 showed elevations in both IL-2 and IFN-γ, along with increased macrophage activity.[19] Macrophages induced by Th1 cytokines, which is the primary response of these vaccines, secrete such pro-inflammatory cytokines as IL-6 and TNF-α.[20]

The primary mediators of inflammation currently studied in the COVID-19 vaccine are IFN-γ, IL-2, and TNF. Both IFN-γ and TNF-α are associated with psychosis, and TNF-α is associated with mania and depression. The primary Th1 response, which generates IFN-γ and IL-2, is particularly interesting, as this has been associated with depression in those with MDD.[3,18] The proposed activation of macrophages with vaccination also merits further investigation, as the stimulation of these macrophages by the Th1 response of the mRNA vaccine would cause a rise in the magnitude of IL-6 and TNF-α.[20] These are both important mediators of psychosis, depression, and mania. The types of pro-inflammatory markers that are elevated after receiving the COVID-19 vaccine are those that have been found to be present during acute worsening of psychiatric illness. Our patients both had worsening depression, mania, and psychosis after vaccination, despite being stable for years on the same medications.

Limitations. The primary limitation of this study is that it is a small case series.

Large randomized, controlled trials (RCTs) are needed to account for confounding variables and selection bias. Other limitations include that the second case involved nonadherence to medication, though this occurred after exacerbation of symptoms postvaccination. The second case also involved atypical features of BD1, being that the patient was diagnosed at the age of 16 years, was relatively stable off-medication for years, was previously stabilized on a relatively low dose of lamotrigine (which is typically effective for mania maintenance but not acute mania), and had significant impairments in attention and memory. However, his drug screens were negative, and he required an antipsychotic and mood stabilizer for stabilization in this most recent hospitalization, consistent with psychotic mania.

Despite the limitations, we believe this study is worth consideration, as it is the first of its kind, and the side effects of COVID-19 vaccination are only just beginning to be understood; we hope that this will spur further research with well-designed studies to help determine if these postvaccination episodes were directly due to the vaccine or simply coincidental in their proximity to vaccination. Until this is elucidated, we cannot recommend against COVID-19 vaccination since, at this time, it appears that the known benefits outweigh these unknown risks. This is especially true in individuals with serious mental illness, who are two times more likely to die from COVID-19 than the general public and, among those over 60 years, four times more likely to die.[21] We also cannot definitively make recommendations against prophylactically increasing medication doses at the time of vaccination until this is further studied.

CONCLUSION

This case series describes mixed episodes with psychotic features that occurred shortly after COVID-19 vaccination in patients with BD1 who had been stable for years on the same medication. Because vaccines have been linked with pro-inflammatory markers, and several of these same markers have been linked with acute psychiatric episodes, it is possible that our patients suffered unintended consequences from the COVID-19 vaccine. We hope this potential link is studied further to determine whether it is causal and, if so, how to best address it (prophylactically and/or after the fact). Our patients stabilized after increasing or adding antipsychotic medication, but this was only after suffering weeks of worsening symptoms that negatively impacted their quality of life and employment. While awaiting more information, we must tailor our care to ensure close follow-up during the postvaccination period to diagnose and treat acute symptoms early to limit adverse patient outcomes.

In this case series, we described two individuals with BD1 that, following years of stability on medications, had acute exacerbations following COVID-19 vaccination. We discussed the possibility that the exacerbations were vaccine-related inflammatory responses, but further studies are required to make this determination. In both cases, remission followed additional medication. Though further research is needed, our cases indicate that clinicians should monitor their patients following vaccination for the potential need of additional medication.

DISCLAIMERS

The views in this article are those of the authors and do not represent a position of Oakland University William Beaumont School of Medicine, Easterseals Michigan, or Beaumont Health.

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