

Understanding Psychosis in a Veteran With a History of Combat and Multiple Sclerosis

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A patient with significant combat history and previous diagnoses of multiple sclerosis and unspecified schizophrenia spectrum and other psychotic disorder was admitted with acute psychosis inconsistent with expected clinical presentations.

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Multiple sclerosis (MS) is an immune-mediated neurodegenerative disease that affects > 700,000 people in the US.¹ The hallmarks of MS pathology are axonal or neuronal loss, demyelination, and astrocytic gliosis. Of these, axonal or neuronal loss is the main underlying mechanism of permanent clinical disability.

MS also has been associated with an increased prevalence of psychiatric illnesses, with mood disorders affecting up to 40% to 60% of the population, and psychosis being reported in 2% to 4% of patients.² The link between MS and mood disorders, including bipolar disorder and depression, was documented as early as 1926, with mood disorders hypothesized to be manifestations of central nervous system (CNS) inflammation.³ More recently, inflammation-driven microglia have been hypothesized to impair hippocampal connectivity and activate glucocorticoid-insensitive inflammatory cells that then overstimulate the hypothalamic-pituitary-adrenal axis.^{4,5}

Although the prevalence of psychosis in patients with MS is significantly rarer, averaging between 2% and 4%.⁶ A Canadian study by Patten and colleagues reviewed data from 2.45 million residents of Alberta and found that those who identified as having MS had a 2% to 3% prevalence of psychosis compared with 0.5% to 1% in the general population.⁷ The connection between psychosis and MS, similar to that between mood disorders and MS, has been described as a common regional demyelination process. Supporting this, MS manifesting as psychosis has been found to

present with distinct magnetic resonance imaging (MRI) findings, such as diffuse periventricular lesions.⁸ Still, no conclusive criteria have been developed to distinguish MS presenting as psychosis from a primary psychiatric illness, such as schizophrenia.

In patients with combat history, it is possible that both neurodegenerative and psychotic symptoms can be explained by autoantibody formation in response to toxin exposure. When soldiers were deployed to Iraq and Afghanistan, they may have been exposed to multiple toxicities, including depleted uranium, dust and fumes, and numerous infectious diseases.⁹ Gulf War illness (GWI) or chronic multisymptom illness (CMI) encompass a cluster of symptoms, such as chronic pain, chronic fatigue, irritable bowel syndrome, dermatitis, and seizures, as well as mental health issues such as depression and anxiety experienced following exposure to these combat environments.^{10,11}

In light of this diagnostic uncertainty, the authors detail a case of a patient with significant combat history previously diagnosed with MS and unspecified schizophrenia spectrum and other psychotic disorder (USS & OPD) presenting with acute psychosis.

CASE PRESENTATION

A 35-year-old male veteran, with a history of MS, USS & OPD, posttraumatic stress disorder, and traumatic brain injuries (TBIs) was admitted to the psychiatric unit after being found by the police lying in the middle of a busy intersection, internally preoccupied. On admission, he reported a week of auditory hallucinations

from birds with whom he had been communicating telepathically, and a recurrent visual hallucination of a tall man in white and purple robes. He had discontinued his antipsychotic medication, aripiprazole 10 mg, a few weeks prior for unknown reasons. He was brought to the hospital by ambulance, where he presented with disorganized thinking, tangential thought process, and active auditory and visual hallucinations. The differential diagnoses included USS & OPD, schizophrenia, schizoaffective disorder and ruled out substance-induced psychotic disorder, and psychosis as a manifestation of MS.

The patient had 2 psychotic episodes prior to this presentation. He was hospitalized for his first psychotic break in 2015 at age 32, when he had tailed another car “to come back to reality” and ended up in a motor vehicle accident. During that admission, he reported weeks of thought broadcasting, conspiratorial delusions, and racing thoughts. Two years later, he was admitted to a psychiatric intensive care unit for his second episode of severe psychosis. After several trials of different antipsychotic medications, his most recent pharmacologic regimen was aripiprazole 10 mg once daily.

His medical history was complicated by 2 TBIs, in November 2014 and January 2015, with normal computed tomography (CT) scans. He was diagnosed with MS in December 2017, when he presented with intractable emesis, left facial numbness, right upper extremity ataxia, nystagmus, and imbalance. An MRI scan revealed multifocal bilateral hypodensities in his periventricular, subcortical, and brain stem white matter. Multiple areas of hyperintensity were visualized, including in the right periaxial region and left brachium pontis. More than 5 oligoclonal bands on lumbar puncture confirmed the diagnosis.

He was treated with IV methylprednisolone followed by a 2-week prednisone taper. Within 1 week, he returned to the psychiatric unit with worsening symptoms and received a second dose of IV steroids and plasma exchange treatment. In the following months, he completed a course of rituximab infusions and physical therapy for his dysarthria, gait abnormality, and vision impairment.

His social history was notable for multiple first-degree relatives with schizophrenia. He reported a history of sexual and verbal abuse and attempted suicide once at age 13 years by hanging himself with a bathrobe. He left home

at age 18 years to serve in the Marine Corps (2001-2006). His service included deployment to Afghanistan, where he received a purple heart. Upon his return, he received BA and MS degrees. He married and had 2 daughters but became estranged from his wife. By his most recent admission, he was unemployed and living with his half-sister.

On the first day of this most recent psychiatric hospitalization, he was restarted on aripiprazole 10 mg daily, and a medicine consult was sought to evaluate the progression of his MS. No new onset neurologic symptoms were noted, but he had possible residual lower extremity hyperreflexia and tandem gait incoordination. The episodes of psychotic and neurologic symptoms appeared independent, given that his psychiatric history preceded the onset of his MS.

The patient reported no visual hallucinations starting day 2, and he no longer endorsed auditory hallucinations by day 3. However, he continued to appear internally preoccupied and was noticed to be pacing around the unit. On day 4 he presented with newly pressured speech and flights of ideas, while his affect remained euthymic and his sleep stayed consistent. In combination with his ongoing pacing, his newfound symptoms were hypothesized to be possibly akathisia, an adverse effect (AE) of aripiprazole. As such, on day 5 his dose was lowered to 5 mg daily. He continued to report no hallucinations and demonstrated progressively increased emotional range. A MRI scan was done on day 6 in case a new lesion could be identified, suggesting a primary MS flare-up; however, the scan identified no enhancing lesions, indicating no ongoing demyelination. After a neurology consult corroborated this conclusion, he was discharged in stable condition on day 7.

As is the case with the majority of patients with MS-induced psychosis, he continued to have relapsing psychiatric disease even after MS treatment had been started. Unfortunately, because this patient had stopped taking his atypical antipsychotic medication several weeks prior to his hospitalization, we cannot clarify whether his psychosis stems from a primary psychiatric vs MS process.

DISCUSSION

Presently, treatment preferences for MS-related psychosis are divided between atypical antipsychotics and glucocorticoids. Some suggest that the treatment remains similar

between MS-related psychosis and primary psychotic disorders in that atypical antipsychotics are the standard of care.¹² A variety of atypical antipsychotics have been used successfully in case reports, including ziprasidone, risperidone, olanzapine, quetiapine, and aripiprazole.^{13,14} First-generation antipsychotics and other psychotropic drugs that can precipitate extra-pyramidal AEs are not recommended given their potential additive effect to motor deficits associated with MS.¹² Alternatively, several case reports have found that MS-related psychotic symptoms respond to glucocorticoids more effectively, while cautioning that glucocorticoids can precipitate psychosis and depression.^{15,16} One review article found that 90% of patients who received corticosteroids saw an improvement in their psychotic symptoms.²

Finally, it is possible that our patient's neuropsychiatric symptoms can be explained by autoantibody formation in response to toxin exposure during his time in Afghanistan. In a pilot study of veterans with GWI, Abou-Donia and colleagues found 2-to-9 fold increase in autoantibody reactivity levels of the following neuronal and glial-specific proteins relative to healthy controls: neurofilament triplet proteins, tubulin, microtubule-associated tau proteins, microtubule-associated protein-2, myelin basic protein, myelin-associated glycoprotein, glial fibrillary acidic protein, and calcium-calmodulin kinase II.^{17,18} Many of these autoantibodies are longstanding explicit markers for neurodegenerative disorders, given that they target proteins and antigens that support axonal transport and myelination. Still Gulf War veteran status has yet to be explicitly linked to an increased risk of MS,¹⁹ making this hypothesis less likely for our patient. Future research should address the clinical and therapeutic implications of different autoantibody levels in combat veterans with psychosis.

CONCLUSION

For patients with MS, mood disorder and psychotic symptoms should warrant a MRI given the possibility of a psychiatric manifestation of MS relapse. Ultimately, our patient's presentation was inconsistent with the expected clinical presentations of both a primary psychotic disorder and psychosis as a manifestation of MS. His late age at his first psychotic break is atypical for primary psychotic disease, and the lack

of MRI imaging done at his initial psychotic episodes cannot exclude a primary MS diagnosis. Still, his lack of MRI findings at his most recent hospitalization, negative symptomatology, and strong history of schizophrenia make a primary psychotic disorder likely.

Following his future clinical course will be necessary to determine the etiology of his psychotic episodes. Future episodes of psychosis with neurologic symptoms would suggest a primary MS diagnosis and potential benefit of immunosuppressant treatment, whereas repeated psychotic breaks with minimal temporal lobe involvement or demyelination as seen on MRI would be suspicious for separate MS and psychotic disease processes. Further research on treatment regimens for patients experiencing psychosis as a manifestation of MS is still necessary.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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