A Man Made Manic:
Levodopa-Carbidopa–Induced Mania in Traumatic Brain Injury

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ABSTRACT

Traumatic brain injury (TBI) has had increased notoriety in light of chronic traumatic encephalopathy in professional sports. However, despite the increased rate at which mood disorders affect this population, there remains little information on management of these disorders. TBI has also been implicated in the development of Parkinson disease, increasing the likelihood that patients may be treated with dopaminergic agents. Management of coexisting pathologies can become challenging, especially when confounded by medication side effects. A case is presented of a 58-year-old man who was admitted to the hospital in a manic state 15 years after having suffered a closed head injury. Several psychiatric admissions during the past 2 years were noted, with various diagnoses including different iterations of bipolar disorder. Among his medications, levodopa-carbidopa was present for an unsubstantiated Parkinson disease diagnosis. His mania resolved after discontinuation of the agent. This case is presented with a review of the relevant literature pertaining to the use of levodopa-carbidopa in this context, the use of other dopaminergic agents, and a biological hypothesis for the potential increased likelihood of manic symptoms in TBI patients who receive levodopa-carbidopa. Currently, there is a lack of research in this area, which emphasizes a need to review treatment guidelines for Parkinson disease patients with TBI.

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In recent years, traumatic brain injury (TBI) has had increased notoriety in light of chronic traumatic encephalopathy in professional sports. However, despite the increased rate and severity at which mood disorders affect this population,[1] there remains a paucity of information on management, with few guidelines and a lack of research.[2] TBI has also been implicated in the development of neuropsychiatric disorders including Parkinson disease (PD) later in the disease course.[3] These disease states arguably have significant overlap in pathophysiology and development, thus a significant number of patients will be treated for them in tandem. Management of coexisting pathologies can become challenging, especially when confounded by medication side effects. Here, the case is reported of a man who presented with a manic episode 15 years after having suffered a closed head injury with a resultant intensive care unit stay. Several psychiatric admissions during the past 2 years were noted, with various diagnoses including different iterations of bipolar disorder (BPD) and unspecified and psychotic variants. Among his medications, levodopa-carbidopa was present for a PD diagnosis unsubstantiated by medical documentation. During his hospital course, his manic symptoms resolved after discontinuation of the dopaminergic agent. Ultimately, we diagnosed him with a medication-induced BPD. At the time of this report, there is little present in the literature to delineate a relationship between levodopa-carbidopa and BPD in the context of TBI. Likewise, there have been no documented instances of the medication inducing manic states in this patient population. This case report emphasizes a need to review treatment guidelines for PD patients with TBI.

CASE REPORT

The patient is a 58-year-old white man with a reported history of BPD, PD, controlled hyperlipidemia, and non–insulin-dependent type 2 diabetes mellitus. He was taking quetiapine 800 mg/night, levodopa-carbidopa 25–100 mg 4 times/day, and buspirone 10 mg 3 times/day in addition to metformin 500 mg/night, atorvastatin 10 mg/day, and ramipril 1.25 mg/day. He presented to the hospital emergency department (ED) with what would be diagnosed as a manic episode (*DSM-5* criteria), featuring decreased need for sleep, hyperverbality, irritability, reckless behavior, and increased goal-directed activity. He was subsequently admitted to the inpatient unit.

The patient had been in an automobile accident 15 years earlier, resulting in a closed head injury and a subsequent prolonged intensive care unit stay. The patient had a state-appointed legal guardian for 3 years and was currently living at a group home. It was reported that he had begun to exhibit mood swings after the automobile accident and had initially been living independently with some care provided by his 2 sons. He had no psychiatric history prior to the accident. We were able to obtain a limited history within our electronic medical records. A computed tomography

Clinical Points

- Patients with traumatic brain injury (TBI) often develop neurodegenerative disorders that may require use of dopaminergic medications known to cause manic symptoms.
- Thorough neurologic evaluations should be conducted and documented in detail before a patient with TBI is diagnosed with Parkinson disease or a parkinsonian syndrome, given the implications of inappropriate treatment.
- Due to the increased risk of mania induction, diagnostic caution and a thorough psychiatric evaluation should be pursued for TBI patients who require treatment with dopaminergic medications (ie, levodopa-carbidopa).

(CT) scan acquired for a mechanical fall 6 years after the accident when the patient was aged 49 years demonstrated age-inappropriate frontal lobe atrophy and deepening of the frontal sulci, which was read by the radiologist as "likely due to chronic ischemic changes." A subsequent CT scan within the year he presented to the ED demonstrated both a progression of the changes and lateral ventricular enlargement—a finding associated with chronic TBI.[4] Lipid profiles, hemoglobin A_{1c}, and blood pressure had been well controlled per all documented records.

At the time we saw the patient, neither of his sons was in contact with him or accessible, and he had no next of kin. The group home staff where the patient resided reported that he had a consistent pattern of agitation and misbehavior, had not been sleeping, and was "rambling and ranting" to himself. They confirmed that he complied with his medication regimen, which they administered to him. Just prior to hospitalization, he became hostile when not provided with cigarettes and reportedly grabbed a knife, threatening to kill himself. He finally left the premises and began knocking on neighborhood doors at which time the police were called.

On the inpatient unit, he was administered the Montreal Cognitive Assessment[5] and scored 9 of 30, suggesting severe cognitive impairment with a score of 1 for naming, 2 for attention, 6 for orientation, and 0 for all other domains. A complete blood count, comprehensive metabolic panel, urinalysis, and blood alcohol and thyroid-stimulating hormone levels were all unremarkable. Given his history, a diagnosis of TBI was made in addition to a bipolar diagnosis. He was given a neurologic examination and found to have no muscular rigidity, parkinsonian tremor, micrographia, hypomimia, or festinating gait. There was, however, the presence of coarse, total-limb tremor in his left arm with no rigidity that appeared volitional, correlating with agitation. His primary care provider was contacted and was unaware of how the patient was diagnosed with PD and had no record of a neurologic evaluation. A possible PD misdiagnosis was ruled, and a decision was made to discontinue levodopa-carbidopa and continue the patient on his home medications. With no further changes to his medication regimen, the patient completed a 10-day hospital course with resolution of his presenting symptoms and was discharged to a nursing home with 24-hour supervision given his severe cognitive disability.

DISCUSSION

There is a paucity of research regarding the treatment of behavioral symptoms in patients with TBI, with a heavy reliance on small-scale studies and case reports[2] and a lack of adequate randomized controlled studies.[6] It is evident in the literature that those with TBI demonstrate an increased propensity for developing mood disorders, with up to 9% of patients developing bipolar and related disorders as part of the disease progression[1] compared with 2.6% in the general population.[7] Although our patient was most likely misdiagnosed and inappropriately treated for PD, his presentation lends itself to consideration of how co-occurrence of these disorders should be treated. TBI has been demonstrated to increase the risk of developing PD. A 2015 study of TBI patients aged 55 years and older found them to be at a 44% chance of increased risk of developing PD 5 to 7 years after the TBI.[3] Biological evidence points to a convergent pathophysiology between mania and PD in the context of TBI. TBI has been demonstrated to chronically increase inflammatory cytokines and potentiate a subacute neuronal inflammation, which may be implicated in its chronic neurodegenerative features.[8,9] Actively manic patients have an increased level of proinflammatory cytokines in the cerebrospinal fluid,[10] and similarly chronic neuronal inflammation has been demonstrated to result in α-synuclein aggregation analogous to that associated with PD.[11]

In light of this information, patients with TBI may be more likely to end up on dopaminergic agents like levodopa-carbidopa for the treatment of PD. There are few data to characterize how this medication may affect TBI patients differently than the general population, particularly regarding emotion and behavior. Literature suggests abhorrent dopamine receptor expression in the brain, possibly as a result of protracted axonal degeneration after a traumatic event,[9,12] may sensitize the TBI-affected brain to dopamine. This dopamine hypothesis may provide a sound explanation as to why patients with TBI are at a substantially increased risk of developing BPD.[3] Levodopa is a dopamine precursor and is converted to dopamine in the body via dopamine decarboxylase,[13] which may explain why its discontinuation correlated with a resolution of manic symptoms in our patient. In the literature, it is notable that discontinuation of methylphenidate, a stimulant medication that primarily works through reuptake inhibition of dopamine, was associated with resolution of manic symptoms after its initiation produced them in an adolescent with TBI.[14] Although levodopa has been associated with behavioral disturbances in the general population and mania in the context of treating PD (with ranging prevalence rates and 1 recent study by Maier et al[15] placing it at 5.6% using a

mania self-rating scale), these phenomena have not been examined or studied in TBI.

It is noteworthy, however, that dopaminergic medications have been and continue to be an area of study for use in TBI, particularly in the arena of physical medicine and rehabilitation. Amantadine, a dopamine potentiator and reuptake inhibitor,[9] has demonstrated utility in aiding cognition and decreasing agitation in patients with both acute and chronic manifestations of TBI,[16] although it has other mechanisms of action at play. Bromocriptine, a dopamine receptor agonist,[9] has been studied with conflicting results, with some indication it may function as a procognitive and increase arousal in the acute setting of TBI,[17] but other data classify it as worse than placebo due to an incidence of agitation during a trial in chronic TBI.[18] Levodopa-carbidopa has been comparatively less studied. One 12-patient study[19] from 1988 observed that a trial of the medication enhanced cognitive and behavioral symptoms during post-TBI rehabilitation. A case report[20] from nearly a decade later found that impulsivity with associated "frontal lobe" behavioral symptoms had been treated successfully with amantadine and levodopa-carbidopa as an adjunct. One study[21] suggests that levodopa-carbidopa may help acceleration of healing from an acute post-TBI vegetative state, although it was implicated in producing hallucinations in the same study.

Our patient was ultimately diagnosed with a *DSM-5* criteria medication-induced BPD, which we denoted was in the context of TBI. We could not be certain, however, as it is possible that levodopa was not the sole cause of the patient's mania, but rather a potentiating factor for mania in a bipolar or psychotic disorder otherwise suppressed by a significant dose of quetiapine. It would likewise be difficult to ascertain without a longer course of observation if the patient's symptoms stemmed from an underlying neurocognitive disorder or dementive process. Since he regained stability upon discontinuation of the levodopa, it was not considered to be in the patient's best interest to modify his regimen further. A levodopa rechallenge may have served as a confirmatory measure, but given the lack of a substantiated PD diagnosis, ethical concerns would have arisen. Although the patient had previously been diagnosed with schizoaffective disorder during a prior admission, symptomatology was poorly delineated in the charting; disorganized behavior included poor hygiene that may have been consistent with severe cognitive impairment. In addition, classical first-rank psychotic symptoms were not noted during his 10-day hospital course. One must also take into account environmental modification and the role it may play in behavioral disturbances, particularly in the context of severe cognitive dysfunction. While we could ensure that our setting was a structured, orderly, and nonhostile environment, that same assuredness may not have been manifest at his group home.

CONCLUSION

Given the lack of information and clinical research present on this subject matter, we cannot definitively say that levodopa-carbidopa may be likely to potentiate a manic episode in a patient with TBI. Other factors existed that may have helped decrease behavioral disturbance in our patient, including the change in setting and presence of a structured, more thoroughly supervised environment. Despite these factors, there is a sound biological hypothesis for implication of the medication, and its discontinuation notably correlated with cessation of manic symptoms in our patient. This case highlights the lack of substantial literature in this area of study and underscores the need for larger-scale studies to delineate the most effective and least harmful approaches to using dopaminergic agents in TBI patients when indicated.

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