Cotard Syndrome Resulting From Valacyclovir Toxicity

To the Editor: Valacyclovir is an antiviral medication used often in the treatment of shingles caused by varicella zoster. Because it is renally excreted, kidney functioning must be assessed to determine proper dosing.[1] Neurotoxicity is an uncommon but serious side effect of improper dosing.[2] We describe a patient with bilateral renal cell carcinoma (RCC) on home hemodialysis who was not given renally adjusted valacyclovir dosing and presented with Cotard syndrome. First described by Jules Cotard in 1882,[3] the syndrome's most common presentations include prominent nihilistic delusions, anxiety, agitation, and sensory impairment. The disorder is not specifically noted in *ICD* or *DSM*, but it would be classified as a delusional disorder (codes F22* and 297.1, respectively). The aim of this case study is to increase vigilance of neuropsychiatric effects of valacyclovir toxicity as well as to educate practitioners on presentation of the phenomena of Cotard syndrome.

Case report. Ms A was a 55-year-old woman with bilateral renal cell carcinoma and a psychiatric history significant for only anxiety. She was brought to the hospital emergency department after a change in mental status. Ms A initially presented with laughing, dancing, and screaming, "I am in Heaven." She was focused on her being deceased and in Heaven throughout the initial assessment. Per family, symptoms had begun the morning of presentation, and it was the first time they had ever witnessed this behavior in Ms A. The patient denied any complaints to the treatment team. Ms A reported no auditory or visual hallucinations or suicidal or homicidal ideations. She was oriented to person but not oriented to time, place, or situation.

Thorough workup was initiated and was significant for acute kidney injury showing elevated BUN (blood urea nitrogen) and creatinine and an abnormal EEG (electroencephalogram), showing moderately severe diffuse encephalopathy without focal, lateralized, or epileptiform discharges. Further collateral information from her family revealed that Ms A was being treated for shingles (varicella zoster) prior to admission and had been prescribed valacyclovir 1,000 mg 3 times a day. Given the patient's history of RCC, valacyclovir should have had a renal dosage adjustment to 500 mg/d. She underwent immediate hemodialysis and received dialysis for 4-hour sessions for 3 consecutive days. Ms A showed marked improvement by day 2 with disappearance of her nihilistic delusions, and she demonstrated a complete return to baseline on day 3 of treatment initiation.

Valacyclovir is the L-valyl ester prodrug of acyclovir.[1] Acyclovir is metabolized and oxidized to 9-carboxymethoxymethylguanine (9-CMMG). A mechanism of neuropsychiatric effects of antiviral toxicity most likely occurs when 9-CMMG crosses the blood-brain barrier and inhibits mitochondrial DNA polymerase, which leads to mitochondrial toxicity and ultimately increased uremic toxicity.[4,5] As acyclovir is the active drug of valacyclovir, cases of Cotard syndrome have been reported with it as well.[6]

A 4-hour session of hemodialysis reduces 9-CMMG levels by 64%. Thus, signs of toxicity should subside with daily hemodialysis sessions. Risk factors that may play a role in neurotoxicity include older age and renal dysfunction.[4]

Cotard syndrome can be a part of several different pathologies, so it is imperative to get a thorough history and collateral information, which will influence the appropriate management plan. Gross structural changes have not proved to be appreciated on imaging, historically.[7] Several mechanisms have been proposed for the syndrome, including decreased volume in the anterior insular cortex.[7] Interoception (conscious awareness of internal sensations) is linked to this area of the brain. Only about 200 cases of Cotard syndrome have ever been documented in the literature. Analysis[6] of cases shows a mean age at onset of 52 years, a preponderance among females, and presence of depression and anxiety as risk factors for individuals to develop Cotard syndrome.

This case was a unique opportunity to witness a rare psychiatric presentation in the setting of a substance toxicity. Further, it showcased the need for providers to be able to recognize neuropsychiatric symptoms and keep a broad, yet reasonable differential diagnosis.

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