Clozapine Toxicity Unveiled: Cerebral Edema as a Rare and Alarming Complication

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Case Presentation: A 40-year-old female with a medical history of schizophrenia, hypothyroidism, and hyperlipidemia was admitted to the Emergency Department with a two- to three-day history of altered mental status. At baseline, the patient was fully independent in activities of daily living and able to engage in coherent conversation. However, in the days leading up to her admission, family and caregivers noted her decreased oral intake, neglect of personal hygiene, and incoherent speech.

The patient had been residing in a group home for the past 4-5 months, where she was prescribed multiple psychiatric medications, including clozapine at 100 mg twice daily. During her hospitalization, she was diagnosed with E. coli bacteremia and acute kidney injury (AKI). She was treated with antibiotics, which led to the resolution of bacteremia, and underwent dialysis for acute tubular necrosis. Despite these interventions, there was no significant improvement in her mental status.

Upon admission, the patient's clozapine serum level was found to be 1788 ng/mL, well above the therapeutic range. The decision was made to discontinue clozapine, and further investigations were pursued. Notably, a brain MRI scan performed showed cerebral edema with evidence of posterior fossa fullness and low-lying cerebellar tonsils, raising concern for a rare and severe complication. Treatment with dexamethasone was initiated, leading to marked improvement in her mental status.

Discussion: Cerebral edema is not a commonly recognized effect of clozapine toxicity. The typical manifestations of clozapine overdose include sedation, hypotension, tachycardia, and seizures, but neurological changes such as cerebral edema are exceedingly rare. In this case, the presence of cerebral edema was intriguing given the lack of alternative etiologies. The elevated clozapine level was likely a contributing factor to the development of the edema, though its exact pathophysiology remains uncertain.

Clozapine is metabolized primarily by the cytochrome P450 system, and factors such as renal impairment, drug interactions, and genetic variations can significantly affect clozapine serum concentrations. The patient's underlying renal dysfunction and the high clozapine serum level likely played a crucial role in the onset of toxicity and subsequent cerebral edema. While clozapine toxicity may cause a range of neurological manifestations, cerebral edema is not widely documented in the literature, making this case particularly noteworthy.

The use of dexamethasone in this case provided symptomatic relief and improved the patient's neurological status, suggesting that cerebral edema may be reversible with appropriate intervention. However, the lack of other clear causes of the edema makes it difficult to attribute this solely to clozapine toxicity, highlighting the need for further research into the potential neurological effects of clozapine overdose.

This case emphasizes the importance of recognizing cerebral edema as a rare yet serious complication of clozapine toxicity. Clinicians should monitor clozapine levels closely, particularly in patients with renal impairment, to mitigate the risk of severe neurological outcomes.

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