



(CASE REPORT)



Rare neurologic sequelae: A case report of toxic metabolic encephalopathy caused by carbamazepine-induced hypovolemic hyponatremia

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World Journal of Advanced Research and Reviews, 2024, 21(01), 2021–2024

Publication history: Received on 09 December 2023; revised on 18 January 2024; accepted on 20 January 2024

Article DOI: <https://doi.org/10.30574/wjarr.2024.21.1.0274>

Abstract

Metabolic or secondary encephalopathies originate from non-cerebral organ system failures, often with multifactorial origins. Toxic-metabolic encephalopathy (TME) results from acute cerebral dysfunction due to metabolic disruptions, including drug effects. TME leads to altered consciousness, from delirium to coma, necessitating intensive care and mechanical ventilation.

This study delves into TME, a reversible brain pathology triggered by extracerebral factors, notably drug-induced disturbances. Clinical presentation involves nonspecific altered consciousness, sometimes with asterixis or myoclonus. Carbamazepine (CBZ), a common antiepileptic medication, is linked to hyponatremia, defined by serum sodium levels below 135 mmol/l.

The complexity of AED-induced hyponatremia is explored through a comprehensive patient analysis, revealing an array of symptoms including altered mentality, seizures, respiratory distress, and even coma or death. The case study dissects a patient's experience with toxic-metabolic encephalopathy secondary to CBZ-induced hypovolemic hyponatremia.

This underscores the need for vigilant monitoring and management of adverse drug reactions, spotlighting the intricate interplay of drug-induced metabolic encephalopathies within clinical practice. The study reinforces the importance of awareness and tailored management strategies to enhance treatment outcomes for individuals with epilepsy.

Keywords: Toxic metabolic encephalopathy; Carbamazepine induced hyponatremia; Anti-epileptic drug (AED); Drug induced metabolic encephalopathy; Adverse drug effect

1. Introduction

Metabolic or secondary encephalopathies are disorders in which a disturbance of cerebral function (encephalopathy) results from failure of some other organ system (e.g., heart and circulation, lungs and respiration, kidneys, liver, pancreas and the endocrine glands); in fact in many cases they are multifactorial in origin.^[1]

Toxic-metabolic encephalopathy (TME) results from an acute cerebral dysfunction due to different metabolic disturbances including medications or illicit-drugs. TME could be defined as a developing brain process secondary to a metabolic disturbance but is often described as multifactorial in origin. This metabolic disturbance can be either innate, very rare, or acquired, most frequently, and is secondary to an organ failure, to altered homeostasis, the deficit or the accumulation of some endogenous or exogenous substances, including medications, illicit drugs or any neurotoxic

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substance. It can lead to altered consciousness, going from delirium to coma, which may require intensive care and invasive mechanical ventilation.^[4]

TME is a potentially reversible pathological process within the brain, arising from an extra-cerebral origin, secondary to different metabolic disturbances including the effect of medications/drugs and their withdrawal.^[4]

The clinical presentation of TME is nonspecific and implies altered consciousness, without, in general, any focal and/or asymmetrical neurological signs. Abnormal movements such as asterixis or myoclonus can be found.^[4]The main drugs which causing toxic metabolic encephalopathy are mentioned in Table 1.

Carbamazepine (CBZ) is a traditional antiepileptic drug (AED) for treating partial seizures, partial seizures with secondary generalization and generalized tonic-clonic seizures.^[3]CBZ is one of the AEDs most likely to cause hyponatremia in patients with epilepsy.^[3]

Hyponatremia is defined as a sodium levels less than 135 mmol/l.^[3] The normal concentration of serum sodium is 135-145 mmol/l.The clinical signs and symptoms of hyponatremia are directly related to the development of cerebral edema, increased intracellular pressure and cerebral hypoxia. Early symptoms of hyponatremia from any cause may include apathy, weakness, muscular cramps, nausea, vomiting, and headache.^[7]

Patients with AEDs-induced hyponatremia develop somnolence, dizziness, lethargy, altered mentality, nausea or vomiting, abnormal behavior, headache, balance difficulties, disorientation, dysarthria, increasing seizures, respiratory distress, coma and even death.^[3]

In this case report, we present a comprehensive analysis of a patient who developed toxic-metabolic encephalopathy secondary to carbamazepine-induced hypovolemic hyponatremia.

Table 1 Main drugs that could lead to toxic metabolic encephalopathy

Antiepileptics	Benzodiazepines, Valproicacid, Barbiturates Phenytoin Gabapentin Lacosamide, Carbamazepine
Psychiatric	Tricyclic antidepressants, Selective serotonin reuptake inhibitors, Neuroleptics, Lithium
Oncologic	Methotrexate, L-asparaginase, 5-fluoro-uracil, Ifosfamide
Immunosuppressants	Calcineurin inhibitors, Tacrolimus
Antimicrobial agents	Betalactams (including carbapenems, cefepime),Fluoroquinolone, Metrodinazole, Linezolid, Foscavir, acyclovir, Interferon alpha, Fluconazole
Miscellaneous	Dopamine agonists, Levodopa, Opioids, Proton pump inhibitors, Baclofen, Loperamide

2. Case description

A male patient, aged 60-year-old came to S.S.I.M.S & RC, Davangere, Karnataka, complaining of decreased responsiveness, fever, and non-bilious, non-projectile, non-blood-tinged vomiting. He had a history of a longstanding psychiatric disorder and had been dealing with seizure episodes for the past 12 years. The patient had been taking 100mg of Carbamazepine orally twice a day for his seizures.

Upon physical examination, the patient exhibited reduced responsiveness, severe vomiting, and experienced one episode of fever and chills. Laboratory tests unveiled a significantly low level of plasma sodium (107mmol/L), indicative of hypovolemic hyponatremia.

Remarkable improvement was noted after discontinuing Carbamazepine. The hyponatremia was addressed through the administration of 3% NaCl infusion. The patient's treatment plan was adjusted, and he was started on oral phenytoin therapy (Eptoin 100mg twice daily) as a replacement for Carbamazepine. Within three days of this new therapy, the hyponatremia was successfully resolved. Furthermore, the metabolic encephalopathy showed resolution within the span of a week.

2.1. Causality evaluation

To assess the drug-adverse reaction relationship, the World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) Scale was used. The adverse drug reaction (ADR) was classified as a probable ADR based on this scale. The classification was due to a laboratory abnormality linked to a significant drop in serum sodium levels. Suspending the use of Carbamazepine resulted in an elevation of serum sodium levels, demonstrating the concept of de-challenge.^[5]

3. Discussion

According to V *et al.*^[4] among the many causes of altered consciousness, toxic-metabolic encephalopathy (TME) is probably the most common evoked diagnosis and also it has initially been proposed as the cerebral consequences of one major organ dysfunction, it has progressively been applied to all hemispheric neurological symptoms without any focal sign.

Neurologists over many years have labeled patients with abnormal response: somnolent, encephalopathic, drowsy, disoriented, and, when agitated, delirious.^[6] As observed in our patient he was having altered sensorium and was not able to recognise the relatives/family members and was having decreased responsiveness.

Hyponatremia can be associated with either hyponatremic encephalopathy or improper therapy of symptomatic hyponatremia. Clinical evidence suggests that the vast majority of brain damage from hyponatremia is associated with untreated hyponatremic encephalopathy, and occurs primarily in a limited number of clinical settings. These include (a) the postoperative state, (b) polydipsia-hyponatremia syndrome, (c) pharmacologic agents, (d) congestive heart failure, and (e) adult immunodeficiency syndrome (AIDS).^[7] In this case study the laboratory reports of patient was indicating of abnormally low levels of plasma sodium levels indicating severe hyponatremia which occurred secondary due to the long term use of the drug carbamazepine.

Patients between 20 and 80 years of age are most likely to suffer from CBZ-induced hyponatremia. It is believed that older patients have lower sodium values.^[3] The mechanisms underlying AEDs-induced hyponatremia have not been fully elucidated. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is believed to be an important reason for the development of AEDs-induced hyponatremia.^[3] In this patient age is also a significant factor for having hyponatremia.

The drugs that can be used for correcting hyponatremia; demeclocycline effectively improves CBZ- and LEV-induced hyponatremia and is used to treat severe hyponatremia caused by SIADH. Lithium is also effective in treating CBZ-induced hyponatremia.^[3] For this patient hyponatremia was corrected by using 3% of NaCl infusion and it was resolved within in 3 days of time.

Management of TME includes symptomatic management including neuroprotective measures and etiological management. Whatever the etiology of TME, management consists in avoiding fever, controlling mean arterial blood pressure, glucose and sodium levels, avoiding hypercarbia but also severe hypocarbia that has been associated with cerebral ischemia.^[4]

Abbreviations

- **TME:** Toxic metabolic encephalopathy
- **AED:** Anti-epileptic drug
- **CBZ:** Carbamazepine
- **SIADH:** Syndrome of inappropriate antidiuretic hormone secretion
- **WHO-UMC:** World Health Organisation-Uppsala Monitoring Centre
- **ADR:** Adverse Drug Reaction

4. Conclusion

In conclusion, the issue of hyponatremia induced by antiepileptic drugs (AEDs) has not received the requisite attention within the realm of epilepsy patient care. Hyponatremia is a prevalent concern among individuals undergoing AED treatment, and its potential adverse effects can often be underestimated in clinical settings due to its subtle and nonspecific symptomatic presentation.

Prior to initiating AED treatment, it is imperative to conduct serum sodium level testing to ascertain the presence of a low baseline sodium level. Clinicians must be cognizant of risk factors such as advanced age, high AED dosages, low baseline serum sodium levels, concurrent use of multiple therapies, and female gender. Regular monitoring of sodium levels on a weekly basis is recommended. In cases where serum sodium levels continue to decline or remain below 125 mmol/L after the commencement of AED therapy, the consideration of drug withdrawal is essential.

This underscores the significance of vigilant sodium level monitoring and tailored patient management strategies to mitigate the potential complications associated with AED-induced hyponatremia. Enhanced awareness and proactive measures can contribute to safer and more effective treatment outcomes for individuals with epilepsy.

Compliance with ethical standards

Acknowledgments

I thank the patient and his family for allowing me to share this case. I'm thankful to Dr. A. P. Basavarajappa (Principal, Bapuji Pharmacy College, Davangere) and Dr. G. L. Prabhushankar (HOD, Department of Pharmacy Practice).

Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of informed consent

Written informed consent was obtained from the patient for publication of the case report.

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