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Hyponatremia-Induced Epileptic Seizure Provoked by Levetiracetam and Pain Medication Intake in a Patient with Central Diabetes Insipidus

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Keywords
Hyponatremia · Epilepsy · Levetiracetam · Diabetes insipidus · Syndrome of inappropriate antidiuretic hormone

Abstract
Introduction: Causes of epileptic seizures are often multifactorial but for an effective therapy, they should be uncovered in detail. ***Case Presentation:*** We present a 67-year-old male patient with a central diabetes insipidus, who experienced a generalized tonic-clonic seizure. The patient was treated with levetiracetam for prevention of further seizures, opioids and non-steroidal anti-inflammatory drugs, i.e., ibuprofen because of severe back pain due to vertebral compression fractures. In this setting, he developed significant hyponatremia and experienced another epileptic seizure. After stopping analgesics and switching from levetiracetam to lacosamide, sodium levels returned to normal and the patient remained free of seizures since then. ***Conclusion:*** The interrelationships of medical therapy, sodium levels and epileptic seizures in the context of central diabetes insipidus are discussed.

Introduction

Hyponatremia induced by anticonvulsive drugs especially sodium channel blockers is quite common, but the mechanisms are often unclear [1]. Several other agents may induce or potentiate the effects on serum sodium levels, such as opioids or non-steroidal anti-inflammatory drugs (NSAIDs) [2–4], which is often considered to be due to syndrome of inappropriate antidiuretic hormone secretion (SIADH).

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Case Presentation

We present an unusual case of a 67-year-old patient, a physician and engaged astrophotographer, with a history of transnasal hypophysectomy for craniopharyngioma 6 years ago, without a relapse in several MRI investigations in follow-up. He was substituted with hydrocortisone 25 mg/daily, levothyroxine 112 µg daily, minirin (desmopressin) via a nasal applicator and transdermal testosterone. He experienced a first tonic-clonic seizure after a bee bite in the left temporal region with a cutaneous reaction, a stressful long-range car drive and additional sleep deprivation. At the time of the first seizure, his sodium levels were in the normal range (140 mmol/L). An MRI of the brain gave a normal result. In addition, he suffered from fractures of eight vertebral bodies and pain medications were prescribed (fentanyl, tramadol, and ibuprofen). For seizure prophylaxis, levetiracetam was recommended at a dose of 500 mg twice daily. Desmopressin dose (once per day) and water intake remained unchanged. Four days later, he experienced a second epileptic seizure (focal aware seizure). Blood analysis showed significant hyponatremia at 124 mmol/L (Fig. 1). He was switched from levetiracetam to lacosamide and analgesic medication was weaned. Normalization of sodium levels was observed in the following seven 7 days up to a sodium of 141 mmol/L (Fig. 1). A second brain MRI also showed normal results. The first EEG 3 days after the second seizure revealed transient focal slow wave activity in left frontotemporal leads. Further laboratory examinations after recovery showed normal values for cortisol (indicating hydrocortisone substitution was adequate), a normal plasma and urinary osmolality and unmeasurable copeptin levels (<2.7 pmol/L). Three more EEGs were normal and no further seizures occurred during follow-up of 3 months.

Discussion

We speculate that the accumulation of several stressors, a bee bite with an allergic reaction [5], a long car drive and sleep deprivation triggered the first seizure. The history of transnasal hypophysectomy 6 years prior may be another risk factor; however, no reports in the literature were found on such an association. In addition, as the patient is an engaged astrophotographer, a chronically disturbed sleeping pattern may have been another influential factor.

The most likely provoking factor of the second seizure was significant hyponatremia. Hyponatremia was most probably caused by the combined effects of levetiracetam with pain medication intake (opioids and NSAIDs). Although rare, similar observations have been previously published in the context of central diabetes insipidus. For instance, a young patient on desmopressin developed severe hyponatremia after combined hydromorphone and ibuprofen intake that only normalized after sequentially stopping both drugs [4]. It is concluded that such combination therapy should only be performed under strict surveillance of serum sodium levels in patients with central diabetes insipidus (i.e., after hypophysectomy) as such patients may be at higher risk of developing significant hyponatremia [4, 6].

Concerning the mechanism of action, opioids and levetiracetam are classically considered to cause hyponatremia by inappropriate release of ADH from the pituitary gland (also known as SIADH). Our case challenges this concept as the patient was totally dependent on desmopressin substitution after transnasal hypophysectomy as evidenced by unmeasurable copeptin levels. Indeed, opioid-induced hyponatremia has previously been described in a patient with central diabetes insipidus [6]. Interestingly, experimental studies in rats suggest that opioids have antidiuretic effects independent of ADH release, even though the precise mechanism of action is still unclear [7]. Other mechanisms beyond SIADH may also underlie the effect of levetiracetam on sodium levels. Although hyponatremia is less common with levetiracetam than with classical sodium channel blockers, it has been repeatedly described in

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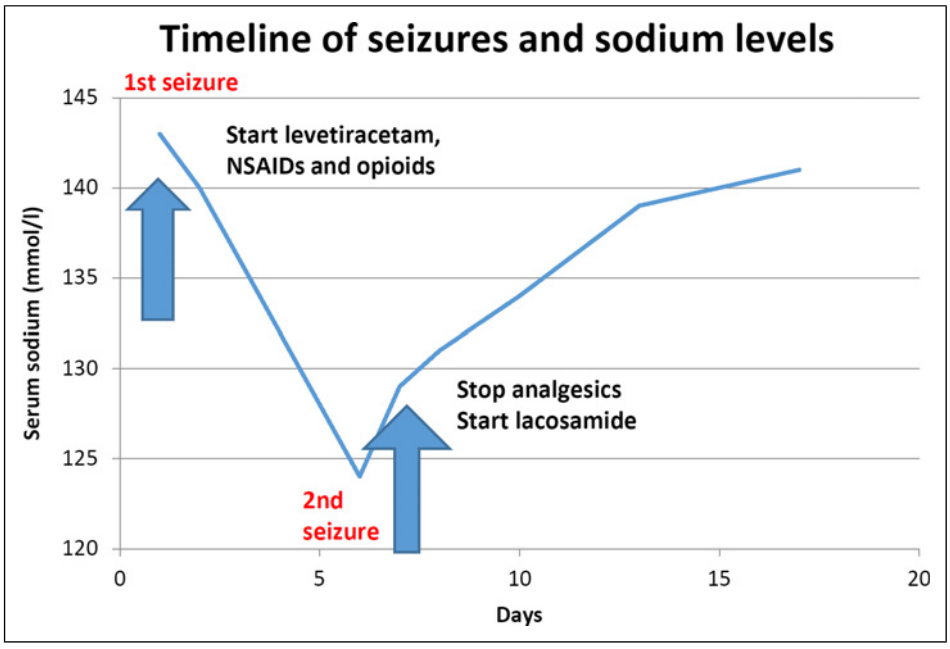

Fig. 1. Timeline of seizures, sodium levels, and change in concomitant medication. The figure shows the timeline of the epileptic seizures with the drop in sodium levels after initiation of levetiracetam and analgesic medications.

the literature. Lacosamide is a possible alternative, with a lower risk of hyponatremia than classical sodium channel blockers [8].

In addition to the effects of opioids and levetiracetam, direct renal effects of ibuprofen may have contributed to the rapid fall in sodium levels in this case. Renal prostaglandins are known to inhibit the effects of ADH on the kidney. By inhibiting renal prostaglandins, NSAIDs like ibuprofen may potentiate the water-retaining effect of ADH at the kidney level, favoring the development of hyponatremia [8].

A limitation of the case is that we could not pinpoint the cause of the seizures on a single mechanism or provoking factor. However, seizures are often multifactorial in their etiology in clinical practice after detailed assessment. The case illustrates that different etiologies of seizures should always be considered and investigated when being confronted with a patient with recurrent seizure episodes, especially in the context of polypharmacy.

It can also be discussed whether an indication for anticonvulsive therapy existed after the first seizure at all [9]. An initial EEG was not performed, as recommended by the guidelines. The second event – propagated by side effects of the anticonvulsant and pain medications – changed the diagnosis from an opportunity seizure to overt epilepsy with all private and professional consequences.

Statement of Ethics

The authors confirm sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation. Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images [the patient under discussion is the author H.N.].

Conflict of Interest Statement

The authors declare that there exists no competing financial interest or personal relationships that could have appeared to influence the work reported in this paper. Unrelated to the paper, MPN reports speaker fees by AstraZeneca and Vifor Pharma, Advisory board and consultancy fees by Boehringer Ingelheim and Pierre Fabre and congress travel support by Pfizer. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000540320).

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Author Contributions

Herbert Naegele had the idea of the paper and wrote a basic manuscript. Michael Rosenkranz carefully edited the manuscript and made worthful corrections from a neurologial standpoint of view. Matthias Naegele searched for the literature, brought it to a scientific context, and wrote the discussion.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Data were available in hospital records and can be submitted on request. Further inquiries can be directed to the corresponding author.

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