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Severe Hyponatraemia under Carbamazepine for Secondary Prophylaxis of Post-Traumatic Epilepsy

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Authors' contributions

This work was carried out in collaboration between all authors. Author JF drafted the manuscript, carried out the literature search, and discussed all aspects with the coauthors. Author CS was treating the patient, collected essential data, and was involved in the discussion of the case. Author CS treated the patient, collected essential data, and was involved in the discussion of the case. Author ES was responsible for the preparation of the radiographic material and contributed to the discussion of the radiological findings. All authors read and approved the final manuscript.

Case study

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ABSTRACT

Aims: Among the antiepileptic drugs (AEDs) applied for secondary prophylaxis of post-traumatic epilepsy (PTE), carbamazepine (CBZ) may cause severe side effects and worsen traumatic brain injury (TBI).
Presentation of Case: Two days after a bicycle accident causing severe TBI, a 23yo female developed a questionable seizure and received CBZ. Since then she required substitution of sodium. Six days after the accident she was extubated. Serum sodium was 123mmol/l. One day after transfer to the general ward, she was found comatose with a serum sodium of 114mmol/l. Cerebral CT showed diffuse cerebral edema. Electroencephalography did not record paroxysmal activity. After replacement of CBZ by levetiracetam, her condition markedly improved with a favourable outcome.
Discussion and Conclusion: CBZ was made responsible for severe hyponatraemia in

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the presented case after exclusion of all other possible causes. Hyponatraemia may trigger the recurrence of cerebral edema after TBI. Hyponatraemia from CBZ may favourably respond to slow substitution of sodium with physiologic saline. CBZ for secondary prophylaxis of PTE may cause hyponatraemia, cerebral edema, and deterioration of pre-existing TBI. Replacement of CBZ by levetiracetame may resolve the condition. CBZ should be used with caution for secondary prophylaxis of PTE in TBI.

Keywords: Cranio-cerebral injury; post-traumatic epilepsy; sodium; side effect; carbamazepine; antiepileptics.

1. INTRODUCTION

Posttraumatic epilepsy (PTE) is a recurrent seizure disorder following traumatic brain injury (TBI, cranio-cerebral injury) [1]. TBI accounts for 10–20% of symptomatic epilepsy in the general population and 5% of all epilepsy [1,2]. Occurrence of seizures after TBI may be categorized as immediate (<24h), early (1-7d), or late (>1w after TBI) [3]. Incidence of early PTE is 3-10% [4,5]. Treatment of symptomatic epilepsy in TBI patients is challenging and usually carried out by antiepileptic drugs (AEDs) such as phenobarbital (PB), phenytoin (PHT), valproic acid (VPA), or carbamazepine (CBZ) [6]. We report a patient with TBI who initially received CBZ and later PHT as secondary prophylaxis of PTE and developed severe side effects.

2. PRESENTATION OF CASE

A 23-year-old female with normal serum sodium levels prior to admission experienced a TBI after a bicycle accident. On admission she vomited and had an initial Glasgow-Coma-scale of 6. She was intubated (hospital day (hd) 1). A CT-scan of the cerebrum and skull revealed a left parieto-temporal subdural and epidural hematoma (4mm) and a parieto-temporal subdural hematoma (4mm) on the right side. Within the frontal and temporo-basal sulci mild blood accumulations, suggesting traumatic subarachnoid bleeding, were detected. There was also mild left temporal contusional bleeding. The left temporo-frontal cortex/white matter border was slightly blurred, thus a contusional edema was suspected. There were non-dislocated fractures of the right os temporale and parietale, os occipitale, os sphenoidale, os nasale, orbital roof, and ethmoidal and frontal sinuses. After a control cerebral CT had shown increase of the right subdural hematoma to 17mm, increase of the left temporal contusional bleeding, and compression of the right ventricle, she was transferred to a hospital with neurosurgical service (hd2). A right osteoplastic trepanation was carried out. Post-operative monitoring of the intra-cerebral pressure revealed normal values. On hd3 she experienced a questionable tonic-clonic seizure, which is why CBZ (600mg/d) was started. At that time she also received arterenol, midazolam, pantoprazole, ceftriaxone, enoxaparin, and potassium-malat. Since then she required continuous substitution of sodium with 0.9% saline infusions at 100ml/h. On hd7 she was extubated, contacted her surrounding, and started to speak. The serum sodium level was 123mmol/l. The carbamazepine level was not determined. She was tired, bradyphrenic, complained about occipital headache, and experienced nausea and vomiting. Differential diagnoses of hyponatraemia considered were vomiting and sweating. Between hd6 and hd9 intra-cerebral pressure continuously increased (Fig. 1), but intra-cerebral pressure values were interpreted as implausible, since the ICP curve was normal, the patient alert, but the intra-cerebral pressure 60mmHg. On hd9 the

intra-cerebral pressure-transducer was removed and she was transferred to the general ward. Sodium substitution was discontinued because of normal serum sodium values.

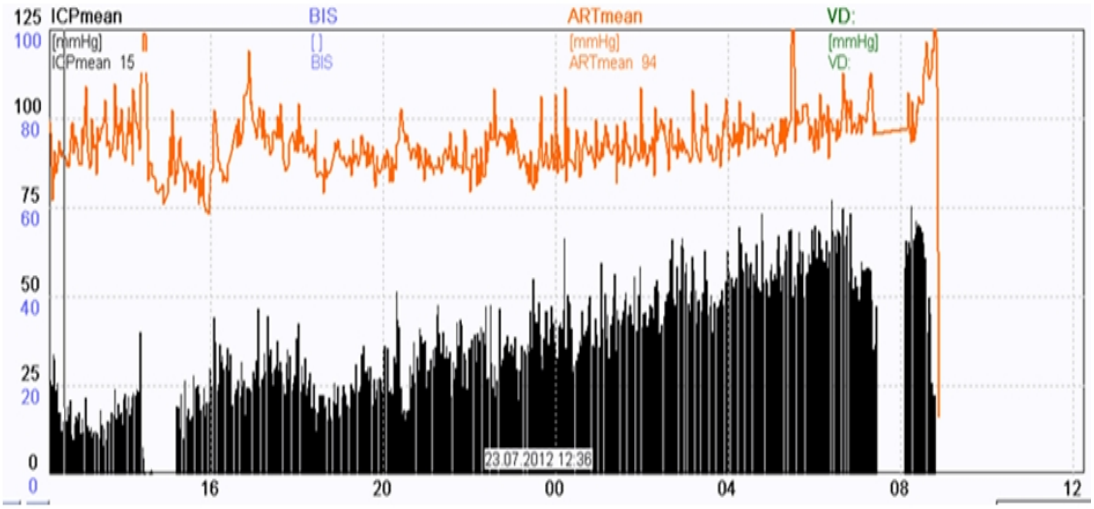

Fig. 1. Intra-cerebral pressure values showing increasing tendency on hd7 and hd8

On hd10 she was found comatose with non-reactive pupils. There was no tongue bite, secessus, or cloni. Serum sodium, however, was reduced to 114mmol/l. Cerebral CT showed generalised cerebral edema (Fig. 2), which is why she was re-intubated and received another intra-cerebral pressure-transducer, which recorded normal values. Though EEG showed diffuse, low-amplitude, irregular alpha-beta activity, with frequent enclosure of high-amplitude alpha-theta groups and delta-waves with the highest amplitude in the frontal regions exclusively, phenytoin (1000mg/d) was added. Phenytoin was chosen since low serum sodium levels did not allow a further increase of the carbamazepine dosage. During the following days serum sodium normalised under continuous sodium substitution. On hd13 Phenytoin was discontinued and CBZ increased to 900mg/d. On hd15 a causal relation between hyponatraemia and cerebral edema was suspected and CBZ replaced by levetiracetam. Cerebral MRI showed subdural hematoma in the right parietal region and contusional lesions in the temporal and frontal regions bilaterally (Fig. 3). No further hyponatraemia or seizures occurred, and she was be successfully extubated on hd22.

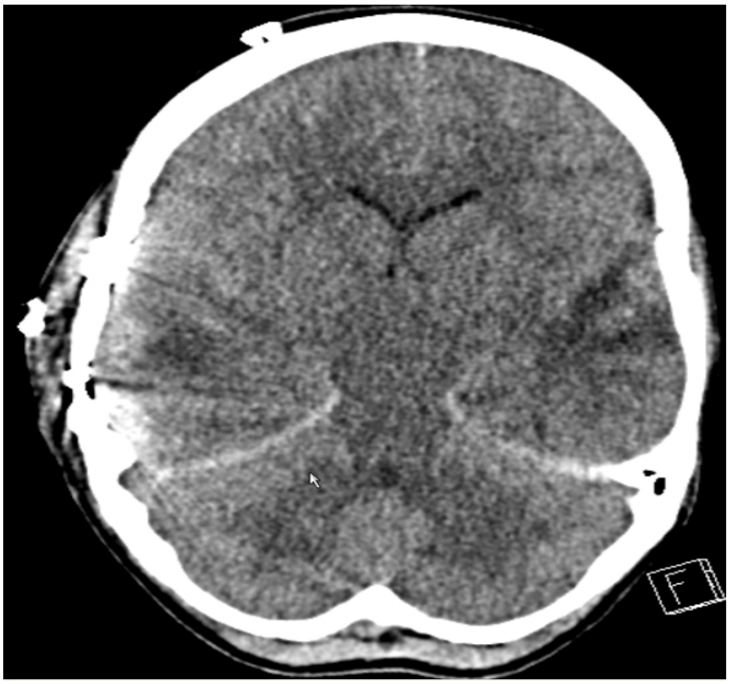

Fig. 2. Cerebral CT scan on hd10 showing diffuse cerebral edema

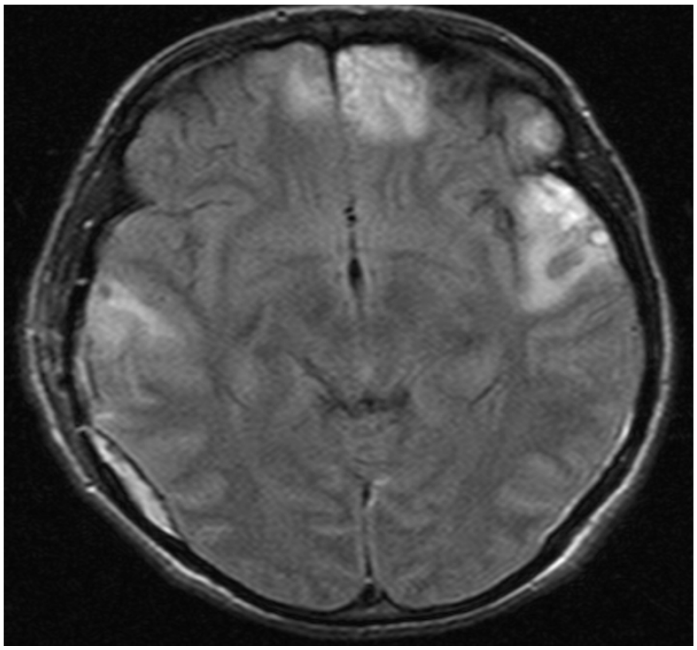

Fig. 3. Cerebral MRI on hd15 showing subdural hematoma in the right parietal region and contusional lesions in the temporal and frontal regions bilaterally

3. DISCUSSION

The presented case is interesting for the development of hyponatraemia under CBZ and consecutive development of cerebral edema during recovery from severe TBI. Whether sudden deterioration of the patient's condition on hd10 is attributable to hyponatraemia alone, to an unwittnessed seizure, or deterioration of TBI, remains speculative, but most likely, hyponatraemia was the sole culprit. Hyponatraemia alone could explain cerebral edema, and her complaints after extubation on hd7. Arguments against a seizure as the explanation for the coma are that there was no tongue bite, no secessus, and absence of paroxysmal activity on EEG. Arguments against a relapse of the TBI are that she has not fallen out of the bed and that cerebral CT did not show ischemia, bleeding, or dislocation of the previously described skull fractures or trepanation.

The cause of hyponatraemia in the presented patient remains speculative but most likely it was due to a side-effect of CBZ. A syndrome of inadequate SDH secretion was excluded as causative, since resolution of hyponatraemia was quickly achieved. There was no history of diarrhoea, vomiting, extreme sweating, metabolic disturbance, or endocrine abnormality prior to TBI and she had not taken drugs in addition to CBZ, which could explain hyponatraemia. Nutrition on the intensive care unit was equalised for sodium but it is possible that sodium intake was too low during the three days between first extubation and second intubation. Hyponatraemia from CBZ may occur already in the first days of administration. The higher the dosage the earlier hyponatraemia may occur.[7] Hyponatraemia may manifest as inappetance, nausea or vomiting, irritability, excessive tiredness, confusion, hallucinations, muscle weakness, or muscle cramps. Possible mechanisms of hyponatraemia due to CBZ include syndrome of inadequate SDH secretion, altered sensitivity to serum osmolality by hypothalamic osmoreceptors, or increased sensitivity of the renal tubules to circulating ADH. Because of the causative relation between hyponatraemia and CBZ, sodium levels need to be closely monitored, as soon as CBZ has been started, particularly in TBI patients. In case hyponatraemia occurs, substitution of sodium needs to be slow and only physiologic saline should be used [8]. Substitution should be slow and hypertonic saline should be strictly avoided not to worsen the problem. Side effects of CBZ other than hyponatraemia include anemia, thrombopenia, bruising or bleeding, hallucinations, depression, suicidal thoughts or behaviour, increased rate of infections, water retention, blood pressure dysregulation, arrhythmias, jaundice, kidney damage, or allergic reactions. PTE may occur in the acute stage (<8d) of a TBI or years later [6]. The mechanism by which PTE develops is unknown but the presence of a cerebral lesion seems to be a prerequisite for the genesis of epileptic activity [6]. Treatment of PTE is under debate but previous studies have shown that phenytoin [5] VPA, [2,5,9] or CBZ [5,10] are regarded effective for secondary prophylaxis of PTE. Alternatives for secondary prophylaxis of PTE include levetiracetame [11,12] and lamotrigine, alone or in combination with levetiracetame [13]. However, there are also reports, which did not show any of the AEDs to be effective for secondary prophylaxis of PTE [14] or studies which showed effectivity of secondary AED prophylaxis only for early but not for late PTE [15]. An invasive therapeutic approach for PTE is PET-guided stereotactic radiosurgery [16].

Concerning the question of primary prophylaxis of PTE, it is still under debate if TBI patients should receive AEDs at all and in case they should receive AEDs, which agents are the most appropriate. According to the Guidelines of the American Society of Neurosurgery, patients with TBI should receive primary AED prophylaxis with phenytoin Chang and Lowenstein [17] according to the American Brain-trauma Foundation, TBI patients should receive phenytoin or CBZ [18,19]. Other AEDs recommended for primary prophylaxis of PTE were topiramate

[20] or lamotrigine [13]. According to the Brain Injury Special Interest Group of the American Academy of Physical Medicine and Rehabilitation, no primary AED prophylaxis of PTE is indicated in TBI patients at all [21].

4. CONCLUSION

This case shows that treatment of early PTE with CBZ may result in severe hyponatraemia causing cerebral edema and deterioration of pre-existing TBI. Replacement of CBZ by levetiracetame resolves side effects of CBZ. CBZ should be used with caution for secondary prophylaxis of PTE in TBI.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Pitkänen A, Bolkvadze T. Head Trauma and Epilepsy. In: Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV, editors. Jasper's Basic Mechanisms of the Epilepsies [Internet]. 4th edition. Bethesda (MD): National Center for Biotechnology Information (US); 2012.
Available: http://www.ncbi.nlm.nih.gov/books/NBK98197/.
2. Benardo LS. Prevention of epilepsy after head trauma: do we need new drugs or a new approach? Epilepsia. 2003;44(suppl 10):27-33.
3. Frey LC. Epidemiology of posttraumatic epilepsy: a critical review. Epilepsia. 2003;10:11–17.
4. Gavranović M, Konjhodzić F, Zubcević S, Catibusić F, Uzicanin S. Posttraumatic seizures - prevention or not. Bosn J Basic Med Sci. 2005;5:58-60.
5. Pagni CA, Zenga F. Posttraumatic epilepsy with special emphasis on prophylaxis and prevention. Acta Neurochir Suppl. 2005;93:27-34.
6. Agrawal A, Timothy J, Pandit L, Manju M. Post-traumatic epilepsy: an overview. Clin Neurol Neurosurg. 2006;108:433-9.
7. Henry DA, Lawson DH, Reavey P, Renfrew S. Hyponatraemia during carbamazepine treatment. Br Med J. 1977;1:83-4.
8. Appleby L. Rapid development of hyponatraemia during low-dose carbamazepine therapy. J Neurol Neurosurg Psychiatry. 1984;47:1138.
9. Ma CY, Xue YJ, Li M, Zhang Y, Li GZ. Sodium valproate for prevention of early posttraumatic seizures. Chin J Traumatol. 2010;13:293-6.

10. Beghi E. Overview of studies to prevent posttraumatic epilepsy. Epilepsia 2003;44(suppl 10):21-6.
11. Jones KE, Puccio AM, Harshman KJ, Falcione B, Benedict N, Jankowitz BT, et al. Levetiracetam versus phenytoin for seizure prophylaxis in severe traumatic brain injury. Neurosurg Focus. 2008;25:E3.
12. Klein P, Herr D, Pearl PL, Natale J, Levine Z, Nogay C, et al. Results of phase 2 safety and feasibility study of treatment with levetiracetam for prevention of posttraumatic epilepsy. Arch Neurol. 2012:1-6. doi: 10.1001/archneurol.2012.445.
13. Kinirons P, McCarthy M, Doherty CP, Delanty N. Predicting drug-resistant patients who respond to add-on therapy with levetiracetam. Seizure. 2006;15:387-92.
14. Schierhout G, Roberts I. Withdrawn: Antiepileptic drugs for preventing seizures following acute traumatic brain injury. Cochrane database Syst Rev. 2012;6:CD000173.
15. Teasell R, Bayona N, Lippert C, Villamere J, Hellings C. Post-traumatic seizure disorder following acquired brain injury. Brain Inj. 2007;21:201-14.
16. Qi ST, Qiu BH, Ouyang H, Peng YP. Clinical features and surgical treatment of posttraumatic epilepsy. Di Yi Jun Yi Da Xue Xue Bao. 2004;24:472-4.
17. Chang BS, Lowenstein DH. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: antiepileptic drug prophylaxis in severe traumatic brain injury: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2003;60:10-6.
18. The Brain Trauma Foundation. The American Association of Neurological Surgeons. The joint section on Neurotrauma and critical care. Role of antiseizure prophylaxis following head injury. J Neurotrauma. 2000;17:549-53.
19. Temkin NR. Preventing and treating posttraumatic seizures: the human experience. Epilepsia. 2009;50(suppl 2):10-3.
20. Dolberg OT, Barkai G, Gross Y, Schreiber S. Differential effects of topiramate in patients with traumatic brain injury and obesity--a case series. Psychopharmacology (Berl). 2005;179:838-45.
21. Practice parameter: antiepileptic drug treatment of posttraumatic seizures. Brain injury special interest group of the american academy of physical medicine and rehabilitation. Arch Phys Med Rehabil 1998;79:594-7.

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