Prevalence and risk factors for hyponatremia in adult epilepsy patients: Large-scale cross-sectional cohort study

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ABSTRACT

Purpose: To evaluate the risk factors and prevalence of hyponatremia among epilepsy patients in relation to use of antiepileptic drugs (AEDs).
Methods: We retrospectively reviewed 14,620 adult patients (aged 18–103 years) and classified them into the following 3 groups: patients without AED treatment (n = 2165, Group I), patients receiving antiepileptic drugs other than carbamazepine (n = 7442, Group II), and patients treated with carbamazepine (n = 5013, Group III). This study did not include the patients receiving oxcarbazepine or eslicarbazepine acetate because these AEDs are not marketed in Japan. Severe hyponatremia was defined as a serum sodium level < 130 mEq/L.
Results: In Groups I, II, and III, the mean sodium level was 140, 139, and 137 mEq/L, respectively. The highest frequency of severe hyponatremia was observed in Group III (7%), and it was much higher than in Group I (0.8%) or Group II (1.2%). In Groups II and III, old age, low body weight, and concomitant use of phenobarbital, benzodiazepines, or antipsychotics were risk factors for hyponatremia. In Group III, the sodium level decreased as the carbamazepine dose increased. At a carbamazepine dose exceeding 600 mg/day, there was 10.9-fold higher prevalence of hyponatremia, and the risk was potentiated by concomitant use of valproate.
Conclusion: The serum sodium level should be monitored carefully when patients are receiving AED polypharmacy combined with antipsychotics. In particular, concomitant administration of valproate enhances the risk of hyperammonemia in patients receiving carbamazepine. These findings may help clinicians to avoid hyponatremia in patients with epilepsy.

1. Introduction

Hyponatremia is a frequent adverse event in patients using antiepileptic drugs (AEDs), and a low serum sodium level can lead to fatigue, headache, vomiting, anorexia, and coma. The normal range of serum sodium is 135–145 mEq/L, while the mean serum sodium level is 129 ± 3.3 mEq/L in patients with symptomatic hyponatremia and it falls to 119 ± 9.1 mEq/L in patients with hyponatremia who develop neurological symptoms [1].

Chronic hyponatremia is associated with fractures [2], which impair the quality of life and the vital prognosis, and severe hyponatremia can occasionally lead to permanent neurological sequelae and death. Moreover, Gankam-Kengne et al. [3] reported that mild hyponatremia (median serum sodium: 133 mEq/L) is an independent risk factor for death, while Halawa et al. [4] suggested that the risk of seizures increases gradually along with a decrease of the sodium level. These reports suggest that the serum sodium level should be monitored regularly in patients receiving AED therapy.

Among AEDs, it is well known that administration of carbamazepine (CBZ) can be associated with a decrease of the serum sodium level. Previous studies have suggested that risk factors for hyponatremia in patients on CBZ therapy include the age [5,6], baseline sodium level [5], dose or blood concentration of CBZ [7–9], and concomitant use of levetiracetam (LEV) [5]. Other concomitant drugs, such as diuretics, levomepromazine, and interferon-alpha, have also been reported to induce hyponatremia [10–12]. However, previous studies have only

Table 1
Characteristics of the subjects.

	Group I (No AEDs)	Group II (AEDs without CBZ)	Group III (AEDs with CBZ)	*P* value
Total number of patients	2,168	7,442	5,013	
Age (years)	37.7 ± 17.3*	36.2 ± 14.4[†]	37.5 ± 14.0	< 0.001
Gender (female, %)	1064 (49.1)	3471 (46.7)	2194 (43.8)	< 0.001
Body weight (kg)	58.9 ± 13.5[§,†]	59.9 ± 14.7[†]	61.1 ± 14.0	< 0.001
Concomitant drugs (%)				
VPA		4,334 (58.3)	1141 (22.8)	
PHT		2,089 (28.1)	1079 (21.5)	
PB		1,745 (23.5)	912 (18.2)	
ZNS		1002 (13.5)	430 (8.6)	
Benzodiazepines		1,838 (24.7)	1415 (28.2)	
LTG		918 (12.3)	434 (8.7)	
LEV		930 (12.5)	515 (10.3)	
Antipsychotics (%)	101 (4.7)	504 (6.8)	541 (10.8)	< 0.001
Serum sodium level (mEq/L)	140.2 ± 2.6[*,†]	139.1 ± 2.9[†]	137.4 ± 4.3	< 0.001
Hyponatremia				
Grade 1 (< 138 mEq/L, %)	186 (8.6)	1528 (20.5)	1536 (30.6)	< 0.001
Grade 3 or 4 (< 130 mEq/L, %)	17 (0.8)	86 (1.2)	350 (7.0)	< 0.001

Significance was determined by ANOVA or the χ^2 test. Post-hoc Scheffé multiple comparison test: *p < 0.001 versus Group II, [†]p < 0.001 versus Group III, [§]p < 0.05 versus Group II. Benzodiazepines were clobazam, clonazepam, nitrazepam, and diazepam.

been case reports or small investigations with fewer than 100 to 1000 subjects, and the results have varied. For example, a high dose of CBZ was associated with an increased risk of hyponatremia in several studies [7–9], but Dong et al. did not find a relationship between the CBZ dose and the serum sodium level [5].

In addition to CBZ, other AEDs are reported to be linked with hyponatremia, including valproate (VPA), lamotrigine (LTG), and LEV [13–16]. However, these reports were based on only 1–4 patients with severe hyponatremia, so the actual incidence of this problem is unknown. According to a population-based case-control study, use of CBZ, phenytoin (PHT), VPA, LTG, LEV, or gabapentin increases the risk of hospitalization for hyponatremia [17]. However, this study was based on a national hospitalization database, which means the patients showed an age bias (mean age: 74 years) and the influence of dosage was not assessed.

Therefore, the present study was performed to evaluate the prevalence and risk factors for hyponatremia in adult epilepsy patients based on data from medical records.

2. Methods

2.1. Subjects and serum samples

The protocol for this study was approved by the ethics committee of the National Epilepsy Center (Shizuoka, Japan). We retrospectively reviewed 14,620 adults with epilepsy aged from 18 to 103 years (6789 women) who underwent measurement of the serum sodium level between January 2006 and December 2017 at our hospital. During the study period, 181,721 serum samples were obtained for routine laboratory tests and sodium levels were measured by using a VITROS5600 autoanalyzer (Ortho Clinical Diagnostics, Tokyo, Japan). Information about the age, gender, body weight, laboratory data (including sodium levels), concomitant AEDs and other drugs, and dosages and measured concentrations of AEDs were obtained for each patient by reviewing the medical records. If multiple measurements of serum sodium were performed in a single patient during the study period, the highest sodium level was used.

Patients were excluded from this study if they had severe infection (CRP > 10 mg/dL), a body weight < 30 kg, or were using diuretics. Patients were also excluded if they had commenced AED therapy within 4 weeks before blood sampling, but those undergoing AED dose adjustment within 4 weeks were included. None of the patients received oxcarbazepine or eslicarbazepine acetate because these AEDs are not marketed in Japan.

We enrolled 14,620 patients and divided them into the following three groups. Group I comprised 2165 patients who were not taking AEDs because they had newly diagnosed epilepsy, suspected epilepsy (including patients eventually found not to have epilepsy), or had completed AED therapy. Group II included 7442 patients using AEDs other than CBZ, while Group III was 5013 patients receiving CBZ with/ without other AEDs. We defined severe hyponatremia as a serum sodium level < 130 mEq/L according to the Common Terminology Criteria for Adverse Events (CTCAE). We also retrospectively reviewed the symptoms of the patients at the onset of hyponatremia.

2.2. Statistical analysis

To compare three or more groups, analysis of variance (ANOVA) was performed with a post-hoc Scheffé multiple comparison test. Comparison of sodium levels among monotherapy AED regimens was done by analysis of covariance (ANCOVA) with adjustment for age and gender, and the significance of intergroup differences was evaluated with a post-hoc Bonferroni test. To identify risk factors for hyponatremia, we initially performed univariate analysis of potential risk factors. Then multiple logistic regression analysis was used to calculate adjusted odds ratios and 95% confidence intervals for the risk of hyponatremia, employing the significant independent variables (P < 0.05) identified by univariate analyses. Results are expressed as the mean ± standard deviation and all analyses were conducted with SPSS software Ver 25.0.

3. Results

3.1. Patient profile

Table 1 compares the clinical characteristics and serum sodium levels of the three groups. There were significant differences of age, gender, and body weight among the groups. In addition, a high rate of concomitant antipsychotic use was noted in Group III (the CBZ -treated group). The mean serum sodium level was significantly lower in Group III than in Group I (no AEDs) or Group II (AEDs other than CBZ). Mild hyponatremia (serum sodium < 137 mEq/L) was found in 8.6%, 20.5%, and 30.6% of Group I, Group II, and Group III, respectively. A high prevalence (7%) of severe hyponatremia (serum sodium < 130 mEq/L) was detected in Group III, and it was much higher than in Group I (0.8%) or Group II (1.2%).

Although symptoms of hyponatremia were not investigated systematically in all of the patients, 156 out of 453 patients (34.3%) with a

sodium level < 130 mEq/L had symptoms such as fatigue, headache, vomiting, anorexia, or coma. Among these 453 patients, 289 patients (63.8%) had mild to severe intellectual disability or dementia and 19 patients (4.2%) were hospitalized for treatment of hyponatremia.

3.2. Influence of the number of concomitant AEDs on serum sodium

The mean serum sodium level was 139.2 ± 2.9 mEq/L in patients on AED monotherapy (n = 5068). In contrast, the mean serum sodium level of patients using 2, 3, and 4 or more AEDs was 138.4 ± 3.7 mEq/L (n = 3663), 137.6 ± 4.1 mEq/L (n = 2373), and 137.1 ± 4.3 mEq/L (n = 1351), respectively, and there was significance difference among these 4 groups (ANOVA; p < 0.001). Post hoc analysis showed significant differences of serum sodium in relation to the use of 2, 3, and 4 or more AEDs compared with AED monotherapy (p < 0.001 by Scheffé test). Thus, the sodium level showed a significant decrease as the number of concomitant AEDs increased.

3.3. Influence of AED monotherapy on serum sodium

This study included 5027 patients receiving AED monotherapy. When we compared serum sodium levels among the AED monotherapy regimens (Table 2), there were significant differences among eight regimens (ANOVA; p < 0.001). Patients on CBZ monotherapy had a significantly lower serum sodium level than other patients. In addition, LTG monotherapy was associated with a significantly lower sodium level than use of VPA, zonisamide (ZNS), or benzodiazepines (p < 0.005 by the Bonferroni test). When a serum sodium level < 130 mEq/L was defined as severe hyponatremia, the frequency of hyponatremia was higher with CBZ monotherapy in comparison with other monotherapy regimens including sodium channel blockers (LTG or PHT).

3.4. Risk factors for hyponatremia in patients with or without CBZ

Univariate analysis identified eight factors associated with severe hyponatremia (serum sodium < 130 mEq/L). Irrespective of concomitant CBZ therapy, factors such as old age, low body weight, and concomitant use of phenobarbital (PB), benzodiazepines, or antipsychotics were associated with an increased risk of hyponatremia. In patients using CBZ, concomitant administration of VPA was a significant risk factor for hyponatremia (Table 4), while it was not a significant factor in patients without CBZ therapy (Table 3). Similarly, the influence of PHT and ZNS on the risk of hyponatremia differed between patients with and without CBZ therapy.

In Group III 4529 out of 5013 patients (90.3%) underwent measurement of both serum sodium level and the CBZ concentration. Analysis of this group revealed a weak negative correlation between the weight-adjusted dose of CBZ (mg/kg) and the serum sodium level (Spearman's correlation: r = -0.25, p < 0.001). The frequency of hyponatremia increased along with the increasing daily dose of CBZ.

3.5. Multiple logistic regression analysis of risk factors for hyponatremia

Finally, multiple logistic regression analysis was performed, and the adjusted odds ratios and 95% confidence intervals were calculated (Table 5). Significant risk factors for severe hyponatremia (serum sodium level < 130 mEq/L) were found to be old age (≥ 60 years), low body weight (< 40 kg), and concomitant use of PB, benzodiazepines, or antipsychotics. In contrast, concomitant use of ZNS reduced the risk of hyponatremia. In this model, use of CBZ was the most important risk factor for hyponatremia and a higher CBZ dosage was associated with an increased risk of hyponatremia, which was potentiated by concomitant administration of VPA.

4. Discussion

In this study, we investigated a large cohort of 12,452 adult epilepsy patients receiving AEDs during a 12-year period and identified the prevalence of hyponatremia. Severe hyponatremia, defined as a serum sodium level < 130 mEq/L, was observed in 436 patients (3.5%). According to a recent report by Intravooth et al., [18] the overall incidence of severe hyponatremia was 3.8% (21/560 patients). In our study, 350 out of 5013 patients (7%) receiving CBZ developed hyponatremia. According to previous reports, the frequency of hyponatremia (serum sodium level ≤ 128 mEq/L) among patients using CBZ was 2.8% in the USA [5] and 7% in the Netherlands [19]. Therefore, our result is within the range of previous findings. We found that CBZ was the AED prescribed most frequently for adult epilepsy patients, and it was also the most important risk factor for hyponatremia. The mechanism by which CBZ induces hyponatremia is not entirely clear, but it is widely accepted that the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) may be important. CBZ may activate the vasopressin 2 receptor, resulting in excessive reabsorption of water from the collecting ducts of the kidneys [1,20].

Among the 453 patients who developed severe hyponatremia during the 12-year study period, the majority (297 patients) did not have typical symptoms of hyponatremia. Because 197 of the 297 asymptomatic patients (66.3%) had intellectual disability or dementia, it may have been difficult for most of them to report adverse events. Both the incidence and prevalence of epilepsy are higher among people with intellectual disability than in the general population, and it is difficult for patients with intellectual disability or dementia to control their water intake. Although our study could not assess the intellectual function of all 12,452 patients, intellectual disability/dementia may be associated with risk of exacerbation of hyponatremia. Accordingly, it is important to identify factors influencing the serum sodium level to prevent hyponatremia in epilepsy patients receiving AED therapy.

In a present study, we demonstrated that AED polypharmacy was associated with a lower serum sodium level. It is often assumed that VPA has the potential to increase the risk of hyponatremia [1]. However, we found that use of VPA was not an independent risk factor for hyponatremia (Table 3), but combination therapy with CBZ and VPA could possibly lead to enhanced interactions that increase the risk of

Table 2
Comparison of the serum sodium level among monotherapy regimens.

Regimen	VPA	CBZ	PHT	PB	ZNS	BZs	LTG	LEV
Number of patients	1,932	1,473	424	355	230	203	169	241
Mean sodium level								
Crude	139.6 ± 2.4	138.4 ± 3.4	139 ± 3.0	139.2 ± 2.5	139.9 ± 2.4	139.5 ± 3.0	138.6 ± 2.3	139.3 ± 2.8
Multivariate*	139.5	138.4	139.1	139.3	139.9	139.8	138.7	139.3
Hyponatremia								
< 138 mEq/L, n (%)	299 (15.5%)	413 (28.0%)	88 (20.8%)	70 (19.7%)	29 (12.6%)	27 (13.3%)	54 (32.0%)	46 (19.1%)
< 130 mEq/L, n (%)	11 (0.6%)	46 (3.1%)	6 (1.4%)	2 (0.6%)	1 (0.4%)	4 (2.0%)	0 (0.0%)	3 (1.2%)

VPA; valproate, CBZ; carbamazepine, PHT; phenytoin, PB; phenobarbital, ZNS; zonisamide, BZs; benzodiazepines, LTG; lamotrigine, LEV; levetiracetam.

* Adjusted for age, gender, and BMI. Post-hoc Bonferroni test: †p < 0.001 versus group I.

Table 3
Univariate analysis of risk factors for severe hyponatremia in Group II (AEDs without carbamazepine).

	Total N = 7,442	No hyponatremia N = 7,356	Hyponatremia N = 86	Odds ratio [95% CI]		P value
Age > 60 years	624	604 (96.8%)	20 (3.2%)	3.39	[2.04-5.62]	< 0.001
Gender (female)	3471	3,439 (99.1%)	32 (0.9%)	0.67	[0.44-1.05]	NS
Body weight < 40 kg	381	349 (91.6%)	32 (8.4%)	11.9	[7.58-18.66]	< 0.001
Valproic acid	4334	4,280 (98.8%)	54 (1.2%)	1.21	[0.78-1.88]	NS
Phenytoin	2089	2,051 (98.2%)	38 (1.8%)	2.05	[1.33-3.14]	< 0.001
Phenobarbital	1745	1,717 (98.4%)	28 (1.6%)	1.59	[1.01-2.50]	< 0.05
Zonisamide	1002	994 (99.2%)	8 (0.8%)	0.66	[0.32-1.36]	NS
Benzodiazepines	1838	1,805 (98.2%)	33 (1.8%)	1.91	[1.24-2.97]	< 0.005
Lamotrigine	918	908 (98.9%)	10 (1.1%)	0.93	[0.48-1.81]	NS
Levetiracetam	930	920 (98.9%)	10 (1.1%)	0.92	[0.47-1.79]	NS
Antipsychotics	504	487 (96.6%)	17 (3.4%)	3.47	[2.03-5.95]	< 0.001

hyponatremia (Tables 4 and 5). CBZ is primarily metabolized by CYP3A4 to yield an active metabolite, carbamazepine-10, 11-epoxide, which has similar or stronger anticonvulsant activity to that of CBZ [21]. An increase of the serum carbamazepine-10, 11-epoxide concentration was reported to be associated with adverse reactions [22]. Concomitant administration of VPA can inhibit hepatic epoxide hydrolase, leading to an increase in the serum level of carbamazepine-10, 11-epoxide [21], and our results suggested that this may elevate the risk of hyponatremia.

The large sample size of the present study also allowed us to assess the effects of AEDs other than CBZ on serum sodium level. We found that use of PB potentially increased the risk of hyponatremia. CBZ, PB, and PHT are hepatic enzyme inducers and these drugs may decrease thyroid hormone levels [23]. Hypothyroidism is associated with an increased plasma level of ADH and decreased renal tubular reabsorption of sodium, which may lead to hyponatremia.

We also showed that use of benzodiazepines was an independent risk factor for hyponatremia. It has been suggested that use of benzodiazepines may increase the risk of pneumonia due to nocturnal and daytime sedation, a higher risk of aspiration, and possible depression of immune function [24]. Therefore, the association of severe hyponatremia with benzodiazepine therapy may be related to a higher frequency of infection.

Among patients on AED monotherapy, use of LTG decreased the serum sodium level to the same extent as CBZ, but none of the patients taking LTG developed severe hyponatremia. A review by Lu et al. [1] showed that three patients who had severe hyponatremia due to SIADH, and two of them were using CBZ. In the present analysis, concomitant use of LTG increased the risk of hyponatremia for patients receiving CBZ, although the difference did not reach statistical significance. Concomitant use of LTG with CBZ may be an enhanced risk of hyponatremia.

Table 5
Multiple logistic regression analysis of risk factors for severe hyponatremia.

Risk factor	OR	[95% CI]	P value
Age (≥60 years)	2.97	[2.23-3.96]	< 0.001
Gender (female = 1)	0.83	[0.67-1.03]	NS
Body weight (< 40 kg)	6.23	[4.52-8.58]	< 0.001
Antiepileptic regimen			
Without carbamazepine*	1.0		
Carbamazepine (≤ 600 mg/day)	3.83	[2.87-5.12]	< 0.001
Carbamazepine (≤ 600 mg/day) + valproic acid	7.25	[5.15-10.22]	< 0.001
Carbamazepine (> 600 mg/day)	10.93	[8.03-14.87]	< 0.001
Carbamazepine (> 600 mg/day) + valproic acid	17.11	[11.62-25.12]	< 0.001
Concomitant antiepileptic drugs			
Phenytoin	0.90	[0.71-1.14]	NS
Phenobarbital	1.37	[1.08-1.72]	< 0.005
Zonisamide	0.58	[0.38-0.88]	< 0.05
Benzodiazepines	1.73	[1.4-2.13]	< 0.001
Use of antipsychotics	4.29	[3.40-5.42]	< 0.001

* Reference category. OR: odds ratio; CI: confidence interval.

We found that concomitant administration of ZNS was associated with a lower risk of severe hyponatremia. ZNS is a weak carbonic anhydrase inhibitor that can induce dyshydrosis, suggesting that reduced sweating may decrease sodium loss in patients using this AED. However, no significant decrease in the risk in patients receiving topiramate was found (Odds ratio 0.86 [95%CI: 0.43–1.70] in Group III). In this group, the mean dose of ZNS and topiramate was 337 mg/day and 186 mg/day, respectively. Thus, low dose topiramate may be associated with low incidence of dyshydrosis.

It is well known that antipsychotics can induce water intoxication and increase the risk of hyponatremia [25]. In the present study,

Table 4
Univariate analysis of risk factors for severe hyponatremia in Group III (AEDs with carbamazepine).

	Total N = 5,013	No hyponatremia N = 4,663	Hyponatremia N = 350	Odds ratio [95% CI]		P value
Age > 60 years	449	395 (88.0%)	54 (12.0%)	1.97	[1.45-2.68]	< 0.001
Gender (female)	2194	2,043 (93.1%)	151 (6.9%)	0.97	[0.78-1.21]	NS
Body weight < 40 kg	179	149 (83.2%)	30 (16.8%)	2.84	[1.89-4.27]	< 0.001
Valproic acid	1141	1,022 (89.6%)	119 (10.4%)	1.84	[1.46-2.31]	< 0.001
Phenytoin	1079	1002 (92.9%)	77 (7.1%)	1.03	[0.79-1.34]	NS
Phenobarbital	912	819 (89.8%)	93 (10.2%)	1.70	[1.32-2.18]	< 0.001
Zonisamide	430	412 (95.8%)	18 (4.2%)	0.56	[0.34-0.91]	< 0.05
Benzodiazepines	1415	1,262 (89.2%)	153 (10.8%)	2.09	[1.68-2.51]	< 0.001
Lamotrigine	434	394 (90.8%)	40 (9.2%)	1.40	[0.99-1.97]	NS
Levetiracetam	515	479 (93.0%)	36 (7.0%)	1.00	[0.70-1.43]	NS
Carbamazepine dose						
> 400 mg/day	2607	2,356 (90.4%)	251 (9.6%)	2.48	[1.95-3.16]	< 0.001
> 600 mg/day	1298	1,135 (87.4%)	163 (12.6%)	2.71	[2.17-3.38]	< 0.001
> 800 mg/day	415	353 (85.1%)	62 (14.9%)	2.63	[1.96-3.53]	< 0.001
Antipsychotics	541	425 (78.6%)	116 (21.4%)	4.94	[3.87-6.31]	< 0.001

concomitant use of antipsychotics with AEDs, especially CBZ, was linked to an enhanced risk of severe hyponatremia. Epilepsy is associated with psychiatric comorbidities, including psychoses, mood disorders, personality disorders, and behavioral disorders, which means that concomitant administration of antipsychotics or mood stabilizers is not uncommon. We recommend routine monitoring of the sodium level in patients using antipsychotics or mood stabilizers with AEDs, especially those on VPA plus CBZ.

The present study had several limitations.

Because of the retrospective design, we could not investigate water intake, diet, exercise, infection, diarrhea, vomiting, and injury, which are all factors that could influence the serum sodium level. Although serum AED concentrations can be a better predictive marker than AED doses, we could not obtain AED steady state concentrations from all patients. Also, we did not evaluate the effect of psychotropic drugs other than antipsychotics. For example, tricyclic antidepressants and selective serotonin reuptake inhibitors are reported to be associated with hyponatremia [26,27]. Moreover, we did not assess the duration of AED therapy. It was reported that the sodium level is influenced within 6 weeks of starting CBZ treatment, but further investigation will be required to determine whether the duration of AED therapy affects the prevalence of hyponatremia.

5. Conclusion

In this study, we identified several risk factors for severe hyponatremia in a large cohort of Japanese adults with epilepsy. We recommend careful monitoring of the serum sodium level when patients are receiving AED polypharmacy combined with antipsychotics. In particular, the combination of high-dose CBZ and VPA may result in enhanced interactions that increase the risk of hyponatremia. These findings may help to reduce adverse events due to AED therapy.

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Declaration of Competing Interest

None of the authors has any conflict of interest to disclose.

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