Article published online: 2021-08-03

High Incidence of Hyponatremia in Patients Operated for Nonsellar/Suprasellar Supratentorial Tumors—A Prospective Observational Study

Ramesh J. Venkatapura[1] Sritam S. Jena[1] Rita Christopher[2] Dhananjaya I. Bhat[3]

[1]Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India
[2]Department of Neurochemistry, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India
[3]Department of Neurosurgery, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India

Address for correspondence Ramesh J. Venkatapura, MD, Department of Neuroanaesthesia and Neurocritical Care, Neurosciences Faculty Center, National Institute of Mental Health and Neurosciences, III Floor, Hosur Road, Bengaluru, Karnataka 560029, India (e-mail: drvjramesh@gmail.com).

J Neuroanaesthesiol Crit Care 2021;8:192–196.

Abstract

Background The incidence of hyponatremia is high in supratentorial tumors. However, most studies of supratentorial tumors have included patients with sellar/suprasellar tumors. It is common knowledge that sellar tumors have higher incidence and severity of hyponatremia. Incidence of hyponatremia is not known if we exclude sellar/suprasellar tumors. Therefore, this study was designed to evaluate the incidence of hyponatremia in supratentorial tumors after excluding sellar/suprasellar tumors.

Methods After institutional ethics committee approval and written informed consent, adult patients with supratentorial tumors (nonsellar/suprasellar) were recruited, and data were collected prospectively. In all patients, serum electrolytes were measured every 2 to 3 days. Hyponatremia was defined as serum sodium of <135 mEq/L. All the patients were followed up till death or discharge from the hospital.

Results A total of 61 patients' data were analyzed. There were 31 male and 30 female patients with an average age of 44 years. There were 23 meningiomas, 36 gliomas, and 2 other tumors. Forty patients (66%) developed hyponatremia during hospital stay. There were 29 mild cases (serum sodium 131–134 mEq/L), 7 were moderate (serum sodium 126–130 mEq/L), and 4 were severe (serum sodium <126 mEq/L). Three hyponatremic meningioma patients died, of which two had mild hyponatremia and one had severe hyponatremia. Duration of hospital stay was longer in hyponatremic patients.

Conclusion The incidence of hyponatremia is high in supratentorial tumor patients after excluding sellar/suprasellar lesions. In the majority of patients, the disturbance is mild. Hyponatremic patients has a longer hospital stay and higher mortality.

Keywords
- supratentorial tumors
- hyponatremia
- neurological deficits

Introduction

Hyponatremia has been observed in 1 to 4% of hospital inpatients, and it is associated with increased mortality.[1,2] It is more common in patients with neurological problems than the general hospital patients.[3] Because of its effects on the injured brain, hyponatremia puts neurosurgical patients at increased risk of complications. The neurological symptoms

published online
August 3, 2021

DOI https://doi.org/10.1055/s-0041-1730043
ISSN 2348-0548

Thieme Medical and Scientific Publishers Pvt. Ltd. A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

of hyponatremia are due to cellular swelling caused by movement of water into the cells through the blood–brain barrier resulting in brain edema. The symptoms can vary from mild to severe. They include nausea, vomiting, confusion, irritability, seizures, increased intracranial pressure, brain herniation, and death.[4,5] In acute and symptomatic hyponatremia, mortality rates may be as high as 18% in medical patients.[6] Mortality is higher in acute hyponatremia (< 48 hours) than the chronic hyponatremia.[5]

Low sodium levels have been observed in approximately 30 to 40% of patients with subarachnoid hemorrhage (SAH), 36 to 58% of patients with bacterial meningitis, and 10 to 35% of patients with traumatic brain injury (TBI).[7-11] The incidence of hyponatremia is between 8 and 35% in brain tumors.[12] Various studies have also shown a high incidence of hyponatremia in supratentorial tumors. However, these studies have included patients with sellar/suprasellar tumors only. It is common knowledge that sellar tumors have a higher incidence and higher severity of hyponatremia.[13,14] The correct incidence of hyponatremia in supratentorial tumors is not known if the sellar/suprasellar tumors were excluded. Therefore, we designed this study to evaluate the incidence of hyponatremia in supratentorial tumor patients after excluding sellar/suprasellar tumors (primary objective) and to evaluate the outcomes of these patients (secondary objective).

Methods

This was a single-center study conducted in a tertiary care academic institution and approval for the study was obtained from the institute ethics committee. In this prospective study, adult patients (>18 years) with nonsellar/suprasellar supratentorial tumors scheduled for intracranial surgery (irrespective of their serum electrolyte status at the time of admission) were recruited over a period of 6 months. To avoid selection bias, the first eligible patient admitted to the hospital from each of the three surgical units every week starting from Monday was included. Written informed consent was obtained from all the patients. If the patients were unable to give consent (due to low Glasgow coma scale), it was obtained from their legal guardians. The patients who refused to give consent were not included in the study and the patients who withdrew the consent later were also excluded from the analysis. In each patient, serum electrolyte levels were measured on every second or third day by the treating team throughout the hospital admission. If the sodium levels were not measured for 3 consecutive days in the routine management of patients, the investigators intervened and ensured that the sodium measurement was done by the treating team. For patients who developed hyponatremia during follow-up, serum electrolyte levels were examined more frequently till sodium value came back within the normal range (135–145 mEq/L). Decisions regarding management of the patients/management of hyponatremia were taken by the treating physicians. Perioperatively, the mannitol was administered at the sole discretion of the treating physician/surgeon. All the patients received normal saline and Ringer's lactate during surgery. Oral intake was started as soon as possible in the postoperative period. Hyponatremia was defined as serum sodium of <135 mEq/L (mild 131–134 mEq/L, moderate 126–130 mEq/L, and severe <126 mEq/L). All patients were monitored till discharge from the hospital or death in hospital.

The following data were collected: patient demographics, comorbidity data and chronic medications, clinical features (documented from the day of admission till discharge/death), fluid intake and output, use of diuretics, and other drugs affecting serum sodium level (e.g., tricyclic antidepressants, carbamazepine, etc.). Liver function tests and renal function tests were measured as and when required. In the event of hyponatremia, treatments given for the correction were recorded. Outcome parameters such as intensive care unit (ICU) admission, duration of mechanical ventilation, durational of ICU stay, duration of hospital stay, and any mortality were noted.

Statistical Analysis

The data were expressed as mean and standard deviation. The median and interquartile range were calculated for the number of mannitol days and day of operation after admission. Shapiro–Wilk's test was used for confirming the assumption of within-group normality for interval scale variables. Independent samples *t*-test and analysis of variance were used for conducting between-group tests for interval scale variables if normality assumption was satisfied. Chi-square test/Fisher's exact test was used to test the significant difference between the groups for nominal variables. The mortality rate, duration of ICU stay, duration of hospital stay, and time required for correction of hyponatremia were calculated. The *p*-value of < 0.05 was considered as statistically significant.

Results

There were a total of 83 eligible patients, of which 13 patients did not give consent, and therefore, 70 patients were recruited. Among the recruited patients, nine patients withdrew consent later. Thus, a total of 61 patients' data were analyzed. The demographic details of the patients are given in ►**Table 1**. No patient was on carbamazepine/oxcarbazepine or antipsychiatry medications. Forty patients (66%) developed hyponatremia during the hospital stay. There were 29 patients with mild hyponatremia (72%), 7 patients with moderate hyponatremia (18%), and 4 patients with severe hyponatremia (10%). A detailed description of the hyponatremic patients is given in ►**Table 2**. Timing of hyponatremia is given in ►**Table 3**. Mannitol infusion did not influence incidence of hyponatremia (►**Table 4**). Hyponatremia increased the duration of patients' stay in hospital compared with their normonatremic counterparts (►**Table 5**).

Recurrence of hyponatremia was seen in eight patients (20%); two patients each from moderate and severe hyponatremia groups and four patients from mild hyponatremia group. None of the patients developed hypernatremia throughout the hospital stay.

Table 1 Demographic and clinical details of patients

	Hyponatremic patients	Normonatremic patients	*p*-Value
Number	40 (65.6%)	21 (34.4%)	
Age (y)	43.8 ± 11.7	44.4 ± 14.4	0.86
Male:female	21:19	10:11	0.72
Diagnosis			
Meningioma (23)	17 (74%)	6 (26%)	0.54
Glioma (36)	22 (61%)	14 (39%)	
Clival chordoma (2)	1 (50%)	1 (50%)	
Admission GCS			
GCS 14–15	38	19	0.38
GCS 9–13	2	2	
GCS 3–8	0	0	
Comorbidities (total no. of patients)	7	2	0.18
Diabetes mellitus	6	1	
Hypertension	5	1	
Hypothyroidism	2	0	
Asthma	0	1	
Day of operation since admission	5 (median) 3–7 (IQR)	3 (median) 2–3 (IQR)	

Abbreviations: GCS, Glasgow coma scale; IQR, interquartile range.

Table 2 Comparison of patients with various grades of hyponatremia

Characteristics	Hyponatremia			*p*-Value
	Mild (131–134 mEq/L)	Moderate (126–130 mEq/L)	Severe (≤125 mEq/L)	
No. of patients (%)	29 (72.5%)	7 (17.5%)	4 (10%)	
Age (y) (mean ± SD)	42 ± 11.1	46.8 ± 9.5	51.25 ± 6.3	0.19
Gender (M/F)	16/13	3/4	2/2	0.8
Diagnosis	Meningioma—10 Glioma—19	Meningioma—3 Glioma—4	Meningioma—4 Glioma—0	
Serum sodium (mean ± SD)	132.8 ± 1.05	128.3 ± 1.7	123 ± 2.7	0.001
No. of patients received treatment	0	2 (28.7%)	4 (100%)	
Duration of hyponatremia (d) (mean ± SD)	1.55 ± 1.38	6.7 ± 4.15	6.5 ±4.2	0.001
ICU admission (*n*)	5	1	2	
Length of hospital stay	10.7 ± 5.1	14.3 ± 7.1	18.6 ± 9.7	0.03
Mortality	2 (6.9%)	0	1 (25%)	

Abbreviations: ICU, intensive care unit, SD, standard deviation.

Table 3 Timing of hyponatremia

Timing of hyponatremia	Number of patients
At admission	13 (32.5%)
Before surgery (excluding hyponatremia at the time of admission)	2 (5%)
Postoperative	25 (62.5%)

Three patients of hyponatremia died. All three had meningioma, and among them, two were recurrent meningioma. All of them presented with hyponatremia at admission (two patients with mild grade and one patient with severe grade), which was corrected after admission to hospital. However, they had recurrent hyponatremia (severity of grade was similar to admission). In all of them, sodium values were normal before they expired. The clinical impression was that the cause of their mortality was neurological rather than hyponatremia precipitating their neurological deterioration.

Discussion

In the current study, we found that the rate of hyponatremia in supratentorial tumors (after excluding sellar/suprasellar

Table 4 Mannitol usage in normonatremic and hyponatremic patients

Characteristics	Normonatremic patients (*n* = 21)	Hyponatremic patients (*n* = 40)	*p*-Value
Mannitol used (*n*)	16 (76.2%)	30 (75%)	1.0
No. of days on mannitol	4 (median) 2.25–7.5 (IQR)	6 (median) 3–8.5 (IQR)	
Started on day of admission (*n*)	5 (24%)	6 (15%)	
Started postoperatively (*n*)	7 (33%)	14 (35%)	

Abbreviation: IQR, interquartile range.

Table 5 Comparison of complications in normonatremic and hyponatremic patients

Characteristics	Normonatremic patients (*n* = 21)	Hyponatremic patients (*n* = 40)	*p*-Value
Seizures (*n*)	1 (4.7%)	6 (15%)	0.65
Neurological deficits (*n*)	3 (14.3%)	15 (37.5%)	0.08
ICU admission (*n*)	1 (4.7%)	8 (20%)	0.15
Duration of hospital stay, d (mean ± SD)	8.57 ± 3.07	12.15 ± 6.34	0.02
In-hospital mortality	0	3	0.19

Abbreviations: ICU, intensive care unit, SD, standard deviation.

tumors) was as high as 66%. However, in the majority of patients (72.5%), it was mild hyponatremia. The neurological deficits were higher, and the duration of hospital stay was longer in hyponatremic patients regardless of severity.

There is no published study on postoperative disturbance of sodium in patients of craniotomy with supratentorial tumors in the recent past. Hyponatremia in neurosurgical patients is commonly discussed in relation to SAH, TBI, and pituitary tumors.[15,16] Sherlock et al[17] reported a 15.8% incidence of hyponatremia in patients with intracranial neoplasms. They have reported only the significant hyponatremia (serum sodium < 130 mEq/L). The results are similar to our study. In our study, significant hyponatremia (serum sodium ≤130 mEq/L) was seen in 18% of patients (11 out of 61). Our study results are also similar to the study by Belzer et al,[16] who retrospectively analyzed 319 children (0–19 years) undergoing the first neurosurgical procedure for an intracranial tumor (excluding primary pituitary tumors). They found that 55% of the children were hyponatremic among whom, 43% had mild hyponatremia (defined as serum sodium 131–135 mEq/L), and 12% had severe hyponatremia (serum sodium <130 mEq/L).

Unfortunately, available studies on etiology and clinical characteristics of hyponatremia with cerebral tumor in adult patients are quite limited. Most of the studies are available with respect to pituitary tumors. The incidence of hyponatremia in adult patients with sellar/suprasellar tumors was 11% postoperatively.[18] In a systematic review of transsphenoidal surgery patients, 4 to 12% incidence of hyponatremia was observed postoperatively.[19] The etiopathogenesis of hyponatremia in neurosurgical patients is quite complex, and our understanding is limited. The pathophysiology was well simplified and summarized in the review by Hannon and Thompson.[15] The causes of hyponatremia are syndrome of inappropriate antidiuretic hormone secretion (SIADH), adrenocorticotropic hormone deficiency, cerebral salt wasting (CSW) syndrome, a combination of these, or inappropriate fluids administration. The SIADH appears to be the more common etiology in neurosurgical patients.[17] SIADH appears more common cause of hyponatremia than CSW in aneurysmal SAH patients.[20] In tumor patients, SIADH is the most common cause of hyponatremia.[15,21] Again in these studies, most patients studied were from pituitary tumors.

Among the hyponatremic patients who presented with neurological deficits, more than 80% had deficits before the onset of hyponatremia. Thus, the most probable cause of neurological deficits in these patients is the effects of tumor itself, and the neurological deterioration might have caused hyponatremia.

Another interesting finding in this study was the absence of association between mannitol usage and hyponatremia. Seventy-five per cent of both hyponatremic and normonatremic patients received mannitol during surgery and in postoperative period. Thus, it is important to understand that avoiding mannitol may not prevent the development of hyponatremia. We do not have a clear explanation for this. However, we cannot draw any conclusion on these data as the aim of the study was not to assess hyponatremia incidence with mannitol usage.

Limitations

In our institute, most of the patients with intracranial tumors were given corticosteroid therapy in the form of dexamethasone, which can have an influence on the sodium. We have not analyzed the use, duration, or dose of dexamethasone in our subset of patients. We have not monitored the daily intake of sodium and output of sodium. that would have given better understanding of the causes of hyponatremia.

Our patients were admitted under three surgical units consisting of three different groups of physicians. We presume that treatment of patients varies with individual physician's decision. Confounders due to this cannot be ignored.

Conclusion

The incidence of hyponatremia is high in supratentorial tumor patients after excluding sellar/suprasellar tumors. The majority of the cases are mild, and in a sizeable number of patients, hyponatremia occurs in the preoperative period. Hyponatremic patients had a longer hospital stay and higher mortality. However, attributing hyponatremia as the cause of higher mortality is difficult. There may be a case for aggressive monitoring of meningioma patients postoperatively in whom there is preoperative hyponatremia.

Conflict of Interest
None declared.

Acknowledgments
We acknowledge with thanks the editorial inputs from Dr. G.S. Umamaheswara Rao, Professor, Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences, Bengaluru, India.

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