Published in final edited form as:

J Neurosurg Pediatr. 2012 May ; 9(5): 524–529. doi:10.3171/2012.1.PEDS11465.

Hyponatremia with intracranial malignant tumor resection in children

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Abstract

Object—Intracranial neoplasms are the second most common childhood cancer, and lead to significant morbidity and mortality. Hyponatremia is a complication associated with neurosurgical procedures, but children undergoing intracranial tumor resection have not been selectively studied. In this study, the authors aimed to determine the incidence and risk factors associated with hyponatremia among children undergoing intracranial neoplasm resection.

Methods—A retrospective cohort was compiled using the 2006 Kids' Inpatient Database to identify children younger than 21 years of age who underwent intracranial neoplasm resection. Hyponatremia was ascertained by diagnosis codes. Bivariate analyses were conducted using chi-square and Mann-Whitney U-tests. Logistic regression models were developed to evaluate factors associated with hyponatremia in bivariate analyses.

Results—Hyponatremia occurred in 205 (8.7%) of 2343 annual weighted cases, and was independently associated with tumor location in the deep brain structures and ventricles compared with the cortical area (adjusted odds ratio [aOR] 2.4; 95% CI 1.17–5.3). Hyponatremia was also associated with obstructive hydrocephalus (aOR 2.7; 95% CI 1.7–4.3) and emergency department admission (aOR 1.7; 95% CI 1.1–2.4). Hyponatremia was significantly associated with mechanical ventilation, ventriculostomy placement, ventriculoperitoneal shunt placement, and sepsis. Hyponatremia was also associated with a significantly longer average length of stay (24.6 vs 10.2 days), higher average charges (\$191,000 vs \$92,000), and a higher percentage of discharges to intermediate-care facilities.

Conclusions—Hyponatremia commonly occurs with resection of intracranial malignant tumors, especially for lesions located in the deep brain and in patients with obstructive hydrocephalus. Hyponatremia was associated with higher morbidity. Further research is needed to develop targeted monitoring and intervention strategies to decrease perioperative hyponatremia and to determine if this could decrease the number of complications in this specialized population.

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Disclosure Author contributions to the study and manuscript preparation include the following. Conception and design: Williams, Bratton. Acquisition of data: Williams, Bratton. Analysis and interpretation of data: all authors. Drafting the article: Williams. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Williams. Statistical analysis: Williams, Simon, Bratton. Study supervision: Bratton.

Keywords

hyponatremia; intracranial neoplasm; oncology; pediatric neurosurgery; obstructive hydrocephalus

As group, brain tumors account for the second most common childhood cancer, and the leading cause of pediatric cancer-related death.²² Most children in whom intracranial neoplasms are diagnosed undergo at least 1 neurosurgical procedure for diagnosis and resection. Hyponatremia is a well-recognized complication in children with acute CNS injuries and following neurosurgery, with a frequency ranging from 4% to 88%, depending on the process.⁴

Hyponatremia in neurosurgical patients has been attributed to a variety of causes, including infusion of hypotonic fluids, diuretics, SIADH, adrenal insufficiency, and cerebral salt wasting.¹⁰ Hyponatremia can cause seizures, encephalopathy, and cerebral edema, leading to secondary brain injury.^{15,20} Hyponatremia has also been associated with longer hospital stays and poor neurological outcome in children with neurological diseases.¹ However, studies have not selectively assessed hyponatremia and its clinical implications in pediatric patients undergoing surgical management of intracranial neoplasms.

The Agency for Healthcare Research and Quality developed the KID to enable analysis of hospital use by children in the US.⁸ We used the 2006 KID to evaluate children treated with surgery for intracranial neoplasms and to determine the incidence of hyponatremia and assess the risk factors and significant associations in this population.

Methods

Study Design and Data

This is a retrospective cohort study conducted using the 2006 KID for pediatric patients with an intracranial malignant tumor resection to determine the prevalence and risk factors for hyponatremia. The KID comprises discharges from 38 state inpatient databases for children 20 years of age and younger, and includes a sample of pediatric discharges from 3739 US hospitals (defined as short-term, nonfederal, general, and specialty hospitals; excluding hospital units of other institutions). The KID's large sample size enables analysis of uncommon conditions and procedures such as primary resection of intracranial tumors.

The KID has a stratified probability sampling design allowing for national estimates in hospitalization use. The database includes patient demographic information, payer, hospital characteristics, up to 15 ICD-9-CM diagnosis codes, up to 15 ICD-9-CM procedure codes, LOS, charges, admission and discharge status, and survival. The data are anonymous and cannot be linked to identifiers. The University of Utah's institutional review board exempts studies using qualified deidentified data sets from human subject review (University of Utah Institutional Review Board, Standard Operating Procedure 401a; http://www.research.utah.edu/irb/guidelines/pdf/sop/IRB_SOP_401a_approved_Feb11-09.pdf).

We searched the KID for all patients with diagnosis codes of 191.0–191.9 for malignant neoplasm of brain, then restricted the group to those with a procedure code for “other excision or destruction of lesion or tissue of brain” (01.59), which specifically excludes brain biopsies or stereotactic radiosurgeries. We further excluded patients with any procedure code for chemotherapy infusion (99.25), because SIADH is associated with several chemotherapy drugs. Cases of hyponatremia were identified as those patients with diagnosis codes of 276.1 for hyponatremia or 253.6 for SIADH. The following ICD-9-CM

diagnosis, procedure, and CCS codes were measured: tumor location (191.0–191.9); benign intracranial neoplasms (225.0–225.2); metastatic lesions to brain or spinal cord and other parts of the nervous system (198.3, 198.4); obstructive hydrocephalus (331.4); ventriculostomy placement (02.2); VP shunt placement (02.34); mechanical ventilation (96.71 for < 96 hours and 96.72 for ≥ 96 hours); TPN (99.15); enteral feedings (96.6); lumbar puncture (03.31); vascular catheterization (38.93); sepsis (CCS 2); pneumonia (CCS 122); seizures (780.3 and CCS 83); blood transfusion (99.04 and CCS 222); MRI of the brain (88.91 and CCS 198); CT scan of the head (87.03 and CCS 177); physical and occupational therapy (93.83 and CCS 212–215); and radiation (CCS 211)—patients with these codes were compared for risk of hyponatremia. The ICD-9-CM diagnosis code 191.0 correlates with tumor location in the deep brain, and includes the hypothalamus, thalamus, basal ganglia, corpus striatum, and globus pallidus.

Statistical Analysis

Unweighted statistical analyses were conducted using SPSS for Windows (version 14), and weighted analyses were conducted with SAS (version 9.2). To account for the complex sampling strategy, national weighted estimates and their SEs were calculated. The finite population correction was used to adjust the SEs because the results were not generalized beyond 2006, and because the KID sample includes a large percentage of the total population of children treated in hospitals in the US.⁹

Summary results were expressed as means or percentages. Bivariate analyses were conducted using chi-square tests of independence and the Mann-Whitney U-test. Logistic regression models were developed, adjusting for factors that were significantly associated with hyponatremia in the bivariate analysis, with results reported as the adjusted odds ratio with 95% confidence intervals. In the multivariate analysis, tumor location was assessed for risk of hyponatremia and grouped by anatomical regions, as follows: 1) cerebral cortex; 2) cerebellum and brainstem; 3) ventricles and deep brain; and 4) overlapping or not otherwise specified. Age in years, LOS, and cost were evaluated as linear terms, with results reported as the mean ± SEM, and the median with 25% and 75% interquartile ranges. The routine discharge category included discharge codes for routine, home health, and short-term facility transfer, and results were not affected if short-term facility transfer was separated. Statistical significance was defined as $p < 0.05$. The Bonferroni adjustment for significance was used when multiple pairwise comparisons were made within groups.

Results

Using the KID weighting function, hyponatremia occurred in 205 (8.7%) of 2343 annual cases. Table 1 compares patients with and without hyponatremia. There was no significant difference in age, sex, or race between groups. Patients with hyponatremia were more likely to be admitted from the ER and to have Medicaid insurance. Among patients admitted from the ER, a statistically significant proportion (39%) had Medicaid insurance ($p < 0.001$) compared with other admission sources. Hyponatremic patients had a significantly longer average LOS (24.6 vs 10.2 days) and higher average cost of hospitalization (\$191,000 vs \$92,000). The percentage of discharges to intermediate-care facilities was significantly higher in patients with hyponatremia, whereas the percentage of routine discharges was significantly lower in those with hyponatremia (both $p < 0.001$); however, hospital mortality was similar ($p = 0.41$).

Among the entire study group, the most common location of malignant tumors was the cerebellum (20%), followed by the ventricles (14%). Hyponatremia varied significantly based on tumor location (Table 2). Patients with tumors located in the ventricles, deep brain, and cerebellum had significantly higher rates of hyponatremia compared with cortical

lesions (all $p < 0.001$). Presence of metastases was not significantly associated with hyponatremia.

Hyponatremia was associated with increased numbers of procedures and complications, as outlined in Table 2. There was a significantly higher rate of total mechanical ventilation, mechanical ventilation for < 96 hours, lumbar puncture, and venous catheterization among patients with hyponatremia. Hyponatremia was associated with sepsis, but there was no difference in patients with pneumonia. No difference was documented in the occurrence of seizures. Unweighted analysis showed a significant increase in TPN administration and receipt of physical or occupational therapy (unweighted data not shown in tables), but these did not achieve statistical significance in the weighted analysis.

Obstructive hydrocephalus, VP shunt placement, and ventriculostomy placement were all significantly associated with hyponatremia, and were associated with tumor location (Table 3). Tumors located in the cortex had the lowest occurrence of obstructive hydrocephalus and the lowest rates of hyponatremia. Tumors located in the ventricles had the greatest risk of obstructive hydrocephalus (62%), followed by cerebellum (49%) and deep brain locations (48%). Similarly to Table 2, tumors located in the deep brain, ventricles, and cerebellum had the greatest rates of hyponatremia. In 217 (82%) children with ventriculostomy placement and 99 (97%) children with VP shunt placement, a diagnosis of obstructive hydrocephalus was made.

A multivariable model of factors associated with hyponatremia is presented in Table 4. In a weighted analysis in which the cortex was used as the reference tumor location, tumors in the deep brain or ventricles were associated with a more than 2-fold increase in the odds of hyponatremia (aOR 2.4, 95% CI 1.1–5.3), as was obstructive hydrocephalus (aOR 2.7, 95% CI 1.7–4.3). Addition of tumor location changed the point estimated for obstructive hydrocephalus by $< 10\%$, so the association with hydrocephalus was not substantially confounded by tumor site. Additionally, factors suggestive of a delay in diagnosis, including admission from the ER (aOR 1.7, 95% CI 1.1–2.4) and Medicaid insurance (aOR 1.6, 95% CI 1.03–2.4) were independently associated with hyponatremia.

Discussion

We found that 8.7% of children hospitalized for acute surgical management of intracranial malignant neoplasms had a diagnosis code for hyponatremia. Location of the tumor in deep brain structures and obstructive hydrocephalus were associated risk factors, portending a more than 2-fold increase in the odds of hyponatremia. Hyponatremia was associated with more procedures and more complications.

The mechanisms leading to hyponatremia in patients with intracranial neoplasms may be multifactorial. Hyponatremia may be more likely to occur with tumors in deep brain locations due to the manipulation of neurons pivotal in the control of vasopressin and natriuretic peptides, either from the tumor or during neurosurgical treatment. Neurons in the supraoptic and paraventricular nuclei of the hypothalamus control the release of vasopressin, and damage to these neurons may be one cause of SIADH. Manipulation of the neurohypophyseal pathways may also result in increased secretion of natriuretic peptides, which have been implicated in the cerebral salt-wasting syndrome.¹⁶ Previous smaller studies found trends toward more severe and higher rates of sodium perturbations with suprasellar, thalamic, and hypothalamic lesions, and during surgeries involving manipulation of the neurohypophysis.^{12,14}

Increases in intracranial pressure have been associated with increased release of vasopressin, and SIADH¹⁰ and may account in part for the increased incidence of hyponatremia among

patients with obstructive hydrocephalus. Previous studies have linked hydrocephalus in children with intracranial neoplasms to adverse long-term neurological deficits and disability.^{13,17,18} However, no studies have evaluated long-term sequelae of hyponatremia alone or associated with obstructive hydrocephalus in pediatric patients with brain tumors.

Hyponatremia can cause seizures, encephalopathy, and cerebral edema, which can all lead to secondary brain injury.²⁰ Thus, hyponatremia may in part account for increased morbidity in this group of patients, as evidenced by longer hospital stays, higher charges, increased numbers of procedures, and more discharges to intermediate-care facilities. However, development of hyponatremia could also reflect more advanced disease, hydrocephalus, or tumor location; our study cannot ascertain whether hyponatremia reflects more complicated disease or accounts in part for worse brain injury. Other studies have noted increased use of hospital resources and worse outcomes associated with hyponatremia. Al-Zahraa et al.¹ evaluated children with various neurological diseases and found that hyponatremia was associated with longer hospital stays and poor neurological outcome. Sherlock et al.¹⁹ reported longer hospital stays among adult neurosurgical patients with hyponatremia. Additionally, Moritz and Ayus¹⁵ reported that children with intracranial neoplasms and those who had undergone any neurosurgical procedure are more likely to develop encephalopathy if hyponatremia was present.

Previous studies of children with intracranial neoplasms have suggested that delayed diagnosis is associated with worse neurological outcomes.²² Our study found an association between hyponatremia and both admission from the ER and Medicaid insurance. Admission from the ER may suggest the presence of more severe symptoms and greater disease progression. Similarly, patients with Medicaid insurance have been shown to delay seeking medical attention and to use the ER for care.²¹ Children with Medicaid insurance have higher use of emergency and inpatient services for many common pediatric problems.^{3,6,11} The association of these factors with hyponatremia may reflect more advanced disease from decreased access to care.

Our study benefited from a large sample size of 2343 weighted cases, which encompasses a large portion of the approximately 4000 new cases of pediatric intracranial neoplasms estimated to occur each year.⁵ However, our study is limited to retrospective analysis of discharge data and diagnosis codes. Completeness of coding cannot be assured in our data; however, procedures such as CT and MRI studies, which would be expected during the hospitalization for intracranial tumor resection, did not vary between groups. The ICD-9-CM code for hyponatremia does not specify the concentration, so the severity and range of sodium derangement are unknown. The number of occurrences of hyponatremia among individual patients is also not available from this deidentified data set. Additionally, our estimate of just under 9% occurrence of hyponatremia may be imprecise because the completeness of coding is uncertain. However, the association of hyponatremia and potential complications confirms the need to monitor sodium concentrations and urine output in these patients.

The ICD-9-CM codes are not specific for tumor type, and the KID data are deidentified, so review of individual patient data is not possible. Our initial cohort was selected based on patients with codes specifically for malignant lesions (ICD-9 CM 191.0–191.9); however, the accuracy of this coding regarding malignancy may be imprecise, as evidenced by the simultaneous coding of benign neoplasm of the brain (ICD-9 CM 225.0) in 3 of our patients. We are unable to determine whether histological type and grade of tumor play a role in the development of hyponatremia.

We do not have data on the timing of hyponatremia in relation to admission or tumor resection; however, we did attempt to limit one known cause of hyponatremia by excluding patients who received chemotherapy during the same admission. We cannot evaluate for clinical therapies such as hypotonic fluid administration or diuretic use, which may cause or exacerbate hyponatremia. Additionally, patients with intracranial neoplasms are frequently treated with high-dose corticosteroids in the perioperative period to decrease brain edema, and we have no information on the use, duration, or dose in our subset of patients. The different types of corticosteroids have varying degrees of mineralocorticoid effects that would serve to increase serum sodium. Additionally, glucocorticoids are known to inhibit vasopressin release,² and patients with adrenal insufficiency have been found to have hyponatremia and SIADH.⁷ The interactions between corticosteroids and sodium are complex, and we are not aware of studies evaluating the impact of corticosteroids on hyponatremia in this population.

Conclusions

We conducted this study to assess the incidence of, risk factors for, and associations with hyponatremia among children hospitalized for intracranial neoplasm resection. Our study highlights hyponatremia as a common complication in children hospitalized for intracranial malignant tumor resection, occurring in 8.7% of the annual cases. Patients with tumors in deep brain structures and with obstructive hydrocephalus showed the largest association, portending a more than 2-fold increase in the odds of hyponatremia. Admission from the ER and Medicaid insurance were also independent risk factors associated with hyponatremia. Hyponatremia was associated with higher morbidity, as evidenced by association with longer LOS, higher hospital charges, more discharges to intermediate-care facilities, and increased numbers of procedures. Further research is needed to develop targeted monitoring and intervention strategies to decrease perioperative hyponatremia, and to determine if this decreases complications and improves outcomes in this population.

Acknowledgments

Dr. Simon is supported by Award No. K23NS062900 from the National Institute of Neurological Disorders and Stroke, the Child Health Corporation of America via the Pediatric Research in Inpatient Setting Network Executive Council, Seattle Children's Center for Clinical and Translational Research, and Clinical and Translational Science Award Grant No. ULI RR025014 from the National Center for Research Resources, a component of the National Institutes of Health. None of the sponsors participated in design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of the National Center for Research Resources or the National Institutes of Health.

Abbreviations used in this paper

aOR	adjusted odds ratio
CCS	Clinical Classification Software
ER	emergency room
KID	Kids' Inpatient Database
LOS	length of stay
SIADH	syndrome of inappropriate antidiuretic hormone secretion
TPN	total parenteral nutrition
VP	ventriculoperitoneal

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TABLE 1

Select demographic information in 2343 children undergoing surgery for brain tumors *

Characteristic	No. w/Hyponatremia (%)	No. w/Normal Na (%)	p Value
no. of patients	205 (8.7)	2138	
female	92 (45)	925 (44)	0.83
age in yrs			0.39
<1	7 (3)	65 (3)	
1–5	77 (38)	612 (29)	
6–10	39 (19)	455 (21)	
11–19	78 (38)	941 (44)	
20	3 (1)	50 (2)	
NR	0	14 (1)	
race			0.65
white	98 (48)	1111 (52)	
black	10 (5)	126 (6)	
other	50 (24)	404 (19)	
NR	47 (23)	497 (23)	
payer			<0.001
Medicaid	80 (39)	573 (27)	
private	119 (58)	1358 (64)	
other	3 (1)	202 (9)	
NR	3 (1)	5 (<1)	
admission source			<0.001
ER	89 (43)	562 (26)	
other	116 (57)	1568 (73)	
NR	0	8 (<1)	
LOS in days			
mean $\pm$ SEM	24.6 $\pm$ 2.8	10.2 $\pm$ 0.5	
median; IQR	15; 9.7–25.8	6; 3.4–10.6	
total charges in dollars			
mean $\pm$ SEM	191K $\pm$ 18K	92K $\pm$ 4K	
median; IQR	145K; 85K–230K	67K; 45K–106K	
discharge disposition			0.002
intermediate care	35 (17)	113 (5)	
death	3 (1)	17 (1)	
routine [†]	167 (81)	2008 (93)	

Abbreviations: IQR = interquartile range; K = thousand; NR = not reported.

* All reported values are rounded to the nearest percent or whole number from weighted analysis, and may not sum to equal totals.

[†] Routine discharges include those listed as routine, home health, and short-term care facility transfer.

TABLE 2

Select clinical features and complications associated with hyponatremia in children undergoing surgery for brain tumors *

Feature or Complication	No. w/Hyponatremia (%)	No. w/Normal Na (%)	p Value
no. of patients	205 (8.7)	2138	
location of tumor			<0.001
frontal	10 (5)	261 (12)	
temporal	7 (3)	186 (9)	
parietal	6 (3)	99 (5)	
occipital	1 (<1)	60 (3)	
deep brain	27 (13)	140 (7)	
ventricles	42 (20)	285 (13)	
cerebellum	49 (24)	412 (19)	
brainstem	11 (5)	133 (6)	
other/overlapping	30 (15)	284 (13)	
NOS	22 (11)	277 (13)	
metastases to nervous system			
brain & spinal cord	14 (7)	58 (3)	0.1
other, including meninges	7 (3)	24 (1)	0.17
mechanical ventilation	41 (20)	119 (6)	0.002
<96 hrs	22 (11)	73 (3)	0.01
96 hrs	19 (9)	52 (2)	0.06
nutrition			
TPN administration	9 (4)	32 (1)	0.20
enteral feedings	14 (7)	60 (3)	0.16
obstructive hydrocephalus	137 (67)	757 (35)	<0.001
ventriculostomy	80 (39)	360 (17)	<0.001
VP shunt	39 (19)	134 (6)	0.001
infection			
sepsis	26 (12)	19 (1)	<0.001
pneumonia	8 (4)	26 (1)	0.11
seizure	50 (24)	486 (23)	0.68
lumbar puncture	37 (18)	149 (7)	0.002
venous catheterization	51 (25)	189 (9)	<0.001
blood transfusion	30 (15)	210 (10)	0.17
imaging			
MRI brain	61 (30)	612 (29)	0.77
CT brain	13 (7)	146 (7)	0.92
PT &/or OT	16 (8)	69 (3)	0.21

* NOS = not otherwise specified; OT = occupational therapy; PT = physical therapy.

TABLE 3

Tumor location related to obstructive hydrocephalus, ventriculostomy, and VP shunt

Tumor Location	Total Patients	Obstructive Hydrocephalus (%)	Ventriculostomy (%)	VP Shunt (%)
cortex	627	58 (9)	35 (6)	8 (1)
deep brain	170	81 (48)	39 (23)	16 (9)
ventricles	327	202 (62)	106 (32)	43 (13)
cerebellum	462	225 (49)	106 (23)	41 (9)
brainstem	144	59 (41)	34 (23)	10 (7)
other/overlapping	313	114 (37)	51 (16)	29 (9)
NOS	299	155 (52)	70 (23)	26 (9)

TABLE 4

Logistic regression model of factors associated with hyponatremia

Factor	aOR (95% CI)
obstructive hydrocephalus	2.7 (1.7–4.3)
tumor location	
cortex	1; reference group
NOS & overlapping	1.5 (0.7–3.0)
cerebellum & brainstem	1.7 (0.7–3.7)
deep brain & ventricles	2.4 (1.1–5.3)
admission source	
ER	1.7 (1.1–2.4)
payer	
Medicaid	1.6 (1.03–2.4)