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CASE REPORT

Central diabetes insipidus and adipsia due to astrocytoma: diagnosis and management

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Abstract Adipsia and/or diabetes insipidus is rarely a direct complication of astrocytoma. We report a young man with recurrence of anaplastic astrocytoma who presented as severe hypernatremia. This case highlights key diagnostic and therapeutic challenges: (1) the interpretation of the response to exogenous vasopressin in a patient with steroid-induced hyperglycemia and (2) the potential risk of brain edema and herniation if excess water is prescribed along with vasopressin supplementation. The patient was successfully managed with prescribed fluid replacement, daily weights, and regular electrolyte monitoring but no exogenous vasopressin for 8 months until he succumbed to his tumor.

Keywords Astrocytoma · Hypernatremia · Hypodipsia · Vasopressin

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Introduction

Hypernatremia is known to be associated with brain tumors, typically in individuals with partial or complete diabetes insipidus who lack access to water. Adipsia is a rare complication of primary brain tumors and typically occurs postoperatively [1, 2]. Primary brain tumors may also result in abnormalities in vasopressin secretion [3–5], but astrocytoma is a rare cause of these disorders [6, 7]. We report a case of severe hypernatremia due to partial central diabetes insipidus and adipsia in a patient with anaplastic astrocytoma and discuss the diagnostic and therapeutic challenges posed in these circumstances.

Case report

Presentation

The patient is a 20-year-old Caucasian man with a history of anaplastic astrocytoma who was diagnosed at the age of 5 years and treated with craniotomy and excision of the tumor. His course was complicated by hydrocephalus requiring the placement of two ventriculo-peritoneal shunts. At the age of 10 years, he developed recurrence of the astrocytoma and underwent radiation therapy that resulted in anterior pituitary dysfunction, including low adrenocorticotropic hormone, thyroid-stimulating hormone, and gonadotropins. He was treated with hydrocortisone, levothyroxine, and transdermal testosterone, and doses were adjusted regularly to maintain serum levels within the respective normal ranges. He did well until the age of 19 years, when he was found to have a 4.4 × 2.3-cm enhancing mass in the pons and several enhancing masses in the basal ganglia.

Dexamethasone was started at 8 mg per day and slowly tapered to 3.5 mg daily to control brain edema. He was treated with temozolomide and completed his fourth cycle of therapy 3 weeks before his neuro-oncology clinic visit.

At the time of presentation, he had exhibited progressive lethargy over 2 weeks. While he was in school, his teachers noted that he was more awake and interactive if urged to drink cold water. While on spring break, his water intake decreased and his parents observed worsening cognition, language, and motor function. There was no nausea, vomiting, or diarrhea, and no prior history of diabetes mellitus. The patient repeatedly denied thirst.

On physical examination, he was lethargic but responsive to verbal commands. His blood pressure was 94/56 mmHg and his heart rate was 99 beats per minute. He was afebrile. There were scars from the previous craniotomies and ventriculo-peritoneal shunt placements. He was oriented to person, place, and time, but his responses were slowed and deliberate. Mucous membranes were dry. Funduscopic examination was benign. His pupils were equal, round, and reactive to light. There were horizontal oscillatory eye movements, a bifacial weakness, and a right hemiparesis.

Admission laboratory values revealed serum sodium to be 180 mM, potassium 3.4 mM, chloride 140 mM, bicarbonate 32 mM, blood urea nitrogen 37 mg/dL, creatinine 1.2 mg/dL, and serum glucose 414 mg/dL. Urine sodium was 62 mM, potassium 26 mM, and chloride 48 mM. Urine osmolality was not available on the admission panel; however, the calculated electrolyte-free water excretion rate was 1.06 L/day.

Magnetic resonance (MR) images showed the previous enhancing pontine lesion with localized swelling and a necrotic center. The masses in the anterior limb of the left internal capsule and basal ganglia remained unchanged. A 6-mm mass was noted in the region of the foramen of Monro (Fig. 1).

Clinical course

Upon admission to the intensive care unit, he was 152.4 cm tall, his weight 90 kg, and his estimated water deficit based on 60 % water per kg body weight and a normal serum sodium of 140 mM was calculated to be 15 L. Because the patient's heart rate and blood pressure were lower than his premorbid average values of 86 bpm and 120/75 mmHg, he was deemed clinically sodium depleted as well. Due to the chronicity of the hypernatremia and pre-existing brain edema, replacement commenced with oral water and intravenous 0.45 % sodium chloride calculated to decrease his serum sodium concentration by no more than 6 mM over the next 12 h (Fig. 2).

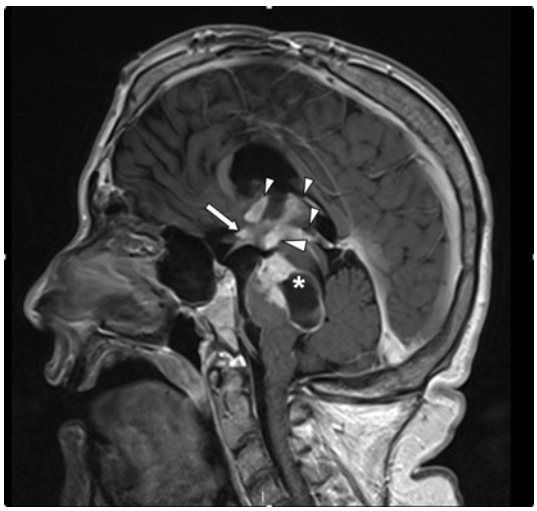

Fig. 1 Magnetic resonance (MR) image of the midline sagittal view of the brain demonstrating the mass with necrosis in the area of the pons (*asterisk*) and basal ganglia (*arrowheads*), as well as the lesion at the foramen of Monro in the area of the subfornical organ (*arrow*)

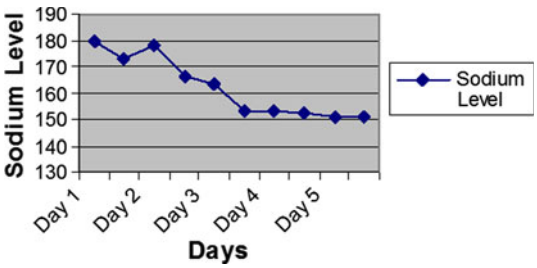

Fig. 2 Graphic representation of serum sodium concentrations during rehydration

The patient was also diagnosed with new onset steroid-associated diabetes mellitus. Repeat serum glucose was 528 mg/dL. He was given insulin aspart 15 U subcutaneously. Within 6 h, his serum glucose declined to 226 mg/dL. The next morning, his serum glucose was 141 mg/dL. On hospital days 2 and 3, he was regulated with 5 U insulin aspart with each meal; the serum glucose ranged from 126 to 238 mg/dL. Thereafter, he was placed on insulin glargine 5 U subcutaneously each evening and metformin 500 mg twice daily, with the serum glucose controlled between 76 and 168 mg/dL during the remainder of the hospitalization. Due to the continued need for dexamethasone therapy after discharge, the patient was discharged on this regimen with good glycemic control as an outpatient (range of serum glucose 81–123 mg/dL).

Testing of his response to exogenous vasopressin was recommended following the validated algorithm described by Miller et al. [8], but without prior overnight dehydration, as the patient was already severely hypernatremic. Table 1 shows the serum and urine sodium and osmolality measured before and after the intravenous administration

Table 1 Serum and urine values before and after the intravenous administration of 4 μg desamino-D-arginine vasopressin (dDAVP)

	Test 1			Test 2	
	Pre-dDAVP	1 h after dDAVP	6 h after dDAVP	Pre-dDAVP	1 h after dDAVP
Serum Na (mM)	174	178	175	155	154
Serum osmolality (mOsm/kgH_2O)	411	391	376	339	336
Serum glucose (mg/dL)	529	226	93	215	156
Urine osmolality (mOsm/kgH_2O)	648	675	912	422	650

of 4 μg desamino-D-arginine vasopressin (dDAVP). At the time of testing, however, he was found to have significant hyperglycemia. Thus, a second trial was performed 3 days later. Plasma vasopressin levels were not obtained in this patient, since the response to exogenous vasopressin was not equivocal [9].

The patient's response was clearly consistent with a diagnosis of acquired hypodipsia with partial diabetes insipidus. When his blood glucose was well controlled, his urine output did not exceed 3 L per day. Because of his multiple brain tumors, particularly within the brainstem, and the potential of developing hyponatremia and aggravating his brain edema if he were given an obligated water intake with exogenous vasopressin, it was decided to avoid using dDAVP as a chronic therapy. Thus, it was decided to maintain the patient solely on a strict calculated water intake regimen designed to maintain his serum sodium concentration in the mild hypernatremic range, 145–150 mM, to minimize brain edema and avoid complications.

When euglycemic, the patient's maximum urine osmolality without exogenous vasopressin varied in the range of 420–494 mOsm/kgH_2O, despite serum sodium levels ranging from 148 to 154 mM. His measured osmotic load based on the total urinary solute excretion on two separate days when blood sugars were <150 mg/dL was 693 and 764 mOsm/day. Thus, assuming a stable obligate osmotic load within this range (~700 mOsm/day), we estimated that he would have a minimum obligate urine volume of 1.4–1.7 L/day to maintain a steady serum sodium level. At the time of discharge, his serum Na was 149 mM, potassium 4.9 mM, chloride 113 mM, bicarbonate 25 mM, blood urea nitrogen 24 mg/dL, and serum creatinine 1.0 mg/dL. His parents were instructed to provide him with 1.7–2.0 L (1.7–2.0 kg) of water daily. This would provide him with roughly the equivalent of his urinary water loss plus 300–400 mL for basal insensible losses from respiration, sweat, and stool. In addition, they were to monitor his weight daily. For each 1 kg of weight loss, they were to give him one additional liter of water. The patient did well on this regimen but eventually became too weak for daily weights. Fluid intake was continued based on the previous schedule, and weekly serum sodium levels were obtained. He was able to maintain a stable serum sodium concentration at home between 148 and 149 mM for 8 months. He eventually died due to progression of his astrocytoma.

Discussion

This case highlights three major issues. First, although more commonly associated with other primary neurologic malignancies [3, 4, 10], astrocytoma can also be associated with diabetes insipidus [6, 11] and/or hypodipsia [7]. Second, lethargy and worsening cognitive function in individuals with central nervous system tumors may be caused by more complex mechanisms rather than just tumor growth and increased intracranial pressure. Third, the diagnosis of partial or complete diabetes insipidus with hypodipsia in the presence of large tumors and dexamethasone therapy necessitates attention to concurrent confounding factors, and management requires the meticulous avoidance of overhydration and potential brain herniation.

The etiology of central diabetes insipidus in children and young adults is highly varied, ranging from autoimmune, vascular diseases, infections, surgical or other trauma [12], and genetic defects [13] to infiltrative diseases such as Langerhans' cell histiocytosis [14, 15] and intracranial tumors [3, 4, 16], including metastases [17]. In the largest reported series of pediatric patients, Maghnie et al. [4] noted that 23 % of cases with central diabetes insipidus occurred with primary brain tumors. Germinoma and craniopharyngioma accounted for two-thirds of the cases; the others occurred after surgical resection. None of the cases was caused by astrocytoma. Likewise, Wang et al. [5] reported 35 children with central diabetes insipidus. Of the 19 patients with brain tumors, only two had suprasellar astrocytomas. Cases with central diabetes insipidus as a complication of astrocytoma are rare and include a report of pleomorphic xanthoastrocytoma in a preadolescent female [6] and gemistocytic astrocytoma in adults [3, 18]. Moreover, to our knowledge, only one case report exists documenting a disordered thirst mechanism with astrocytoma [7]. Our patient manifested both of these disorders, which appeared to have developed virtually simultaneously

late in his 15-year course. Anterior pituitary dysfunction predated the adipsia and diabetes insipidus by 10 years, and was likely a result of radiation therapy at that time. Cranial irradiation predisposes to injury of the anterior pituitary but spares the neurohypophysis, even in follow up as long as 10–12 years following radiation [19, 20]. In a series of 26 patients who received cranial irradiation for extrasellar tumors, none developed diabetes insipidus, although a variety of anterior pituitary disorders were observed [21]. Thus, the timing of our patient's symptoms and hypernatremia and the new MR findings are most consistent with direct tumor injury to the organum vasculosum of the lamina terminalis and loci in the vicinity of the third ventricle, which encompass the subfornical organ and are located in the region of the foramen of Monro (Fig. 1). The tumor involvement of these structures was first demonstrated in our patient approximately 10 weeks prior to presentation. By providing him with water during school sessions ostensibly to keep him alert, his teachers inadvertently treated his osmoregulatory dysfunction, which only came to light after he was on school break.

The organum vasculosum of the lamina terminalis and subfornical organ are established key areas for thirst perception, fluid-seeking behavior, osmoregulation, and vasopressin secretion [22]. Experimental models with ablative lesions of the subfornical organ display adipsia or hypodipsia [23], and those with lesions of the lamina terminalis and region anteroventral to the third ventricle have impaired response to osmotic stimulation and impaired vasopressin secretion [24]. The importance of thirst and drinking is typically overshadowed by defects in vasopressin secretion and urinary concentration. However, this case demonstrates that water intake is crucial to maintaining water balance.

Patients who develop central diabetes insipidus due to brain tumors typically present with polydipsia and polyuria [25], although hypernatremia may be an initial sign [7]. However, if the neural pathways involved in thirst sensation and drinking behavior are also interrupted, primary hypodipsia may obscure the diagnosis. If the water deficit is large enough to result in sufficient intravascular volume depletion to activate baroreceptors [26] and/or if vasopressin secretion is only partially impaired, then the polyuria may also be less evident. Steroids given to treat brain edema may result in hyperglycemia, and the resultant polydipsia and polyuria and even hypernatremia may be misattributed to osmotic diuresis. In addition, glucocorticoids attenuate vasopressin secretion both in vitro [27] and in vivo [28]. Our patient's tachycardia and relatively low blood pressure suggest volume depletion that is further corroborated by the elevated serum creatinine and contraction alkalosis. Notably, he had hyperglycemia but no ketoacidosis. Had the patient not been adipsic, his partial diabetes insipidus could well have gone undiagnosed for a longer period of time.

Concurrent hyperglycemia also interferes with the diagnosis of diabetes insipidus due to impairment of the renal water reabsorption during osmotic diuresis. This was clearly evident in this patient's urinary concentrating response when dDAVP was inadvertently given prior to normalization of his serum glucose. Urinary osmolality increased to 912 mOsm/kgH_2O only after the serum glucose was normalized 6 h after receiving dDAVP. At that time, the collecting ducts would still have been under the influence of dDAVP, whose half-life is roughly five times longer than the endogenous hormone, with an average duration of action of roughly 10 h [29]. The second test corroborated the diagnosis of partial diabetes insipidus with a maximum urine osmolality of only 422 mOsm/kgH_2O, despite a serum sodium concentration of 155 mM and a >50 % rise in urine osmolality in response to dDAVP [9]. Moreover, hyperglycemia accounted for the apparent delay in the correction of his hypernatremia during the first 24 h due to water shifting intracellularly as glycemic control was reestablished. Thereafter, near euglycemia was established and serum sodium improved at a rate of ~4 mM/day and the patient suffered no ill effects. Although it might be expected that neurons and glia chronically exposed to hypertonic conditions would accumulate organic osmolytes to maintain optimal cell volume [30], the care team elected to maintain his serum Na level at roughly 148–150 mM rather than correct it to 140 mM because of persistent concern over the potential expansion of the pontine mass and proximity of the brainstem to bony structures.

Guidelines for the chronic management of patients with brain tumors have largely focused on the treatment of either transient postsurgical diabetes insipidus [12] or chronic diabetes insipidus with hormone replacement [25, 29]. The concurrent existence of adipsia and central diabetes insipidus with persistent brain masses poses an added challenge. Therapy with dDAVP is the standard treatment to correct the urinary concentrating defect due to complete or partial lack of endogenous vasopressin. When the thirst mechanism is intact, the risk of hyponatremia is low. However, when thirst perception is dysfunctional, the risk of administration of excess water along with exogenous dDAVP carries a real risk of hyponatremia and brain herniation, especially in patients with masses within the brainstem. Chlorpropamide has been used to restore drinking behavior in individuals with hypodipsia and diabetes insipidus [1, 2]. These individuals invariably had essential hypernatremia, a condition with dysregulation of osmotic vasopressin release but normal vasopressin response to baroreceptor stimulation [31, 32], rather than brain tumors. This patient's baroreflex-mediated vasopressin release was not formally

tested, but he was not able to concentrate his urine and developed hypernatremia despite relative hypotension and volume depletion at the time of admission. This issue of brain edema and herniation was of particular concern in this patient due to the presence of a tumor in the brainstem, the tendency for edema to occur disproportionately in the area of tumors, and the proximity of the brainstem to bony structures. Since his glycemic status varied with his dexamethasone dosage and his partial central diabetes insipidus rarely resulted in a urine output >3 L/day when his serum glucose was controlled, he was treated solely with water replacement calculated as his fixed requirement of 1.5 L/day (based on daily osmotic losses of ~700 mOsm/day with a maximum urine osmolality of 400 mOsm/kgH_2O) plus replacement of any additional deficit assessed as weight loss from his baseline. His parents meticulously followed explicit directions for water replacement, and the patient's serum sodium level remained stable at the target of 148–149 mM on multiple evaluations during the following 8 months.

In cases where central diabetes insipidus is present with an intact thirst mechanism, the risk of hyponatremia and brain edema will be low, since thirst and, hence, water ingestion, will be suppressed when plasma osmolality is low. Then, the use of exogenous vasopressin or dDAVP is considered to be the standard of care and provides protection against polyuria and dehydration. In contrast, when adipsia occurs with diabetes insipidus, it is also necessary to prescribe water intake. Under these circumstances, there is a finite risk of acutely administering excessive water during antidiuresis induced by exogenous vasopressin. Such an individual will not be able to sense the need to adjust his water intake. Moreover, protection via renal escape from antidiuresis occurs only under chronic excess vasopressin [33]. Thus, there would be less defense against the consequences of acute hypo-osmolality. In hospitalized patients, plasma sodium and/or osmolality can be monitored closely during therapy with fluids and vasopressin, and adjusted accordingly. For chronic therapy in the adipsic diabetes insipidus patient, the risks (hyponatremia, brain edema, and herniation) and benefits (resolution of polyuria, avoidance of dehydration) of exogenous vasopressin should be carefully considered.

In conclusion, astrocytoma can cause hypodipsia and central diabetes insipidus. The absence of complaints of polydipsia and polyuria may be misleading. Hypernatremia, even when associated with steroid-induced hyperglycemia, should be thoroughly investigated for the presence of diabetes insipidus once glycemic control is established. Long-term therapy should balance the benefit of fluid therapy and/or exogenous vasopressin supplementation versus the risk of brain edema and herniation and ease of compliance. If the patient is not burdened by excessive urine output, then strict fluid intake and careful monitoring of weight and electrolytes may be a viable therapeutic option. If the thirst mechanism is intact, then the risk of overhydration and brain edema with exogenous vasopressin therapy for diabetes insipidus will be low. If urine output is excessive and there is concurrent adipsia such that water intake must be prescribed, then the dosing of exogenous dDAVP once daily may permit escape from antidiuresis and the risk of overhydration and life-threatening brain edema.

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Conflict of interest All authors declare that no conflict of interest exists.

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