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An exhaustive battle of salt: A challenging case of Adipsic Diabetes Insipidus following resection of Craniopharyngioma

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Abstract

Introduction :

Even though rare, Adipsic Diabetes Insipidus (ADI) is a potentially life-threatening complication of craniopharyngioma: due to the mass effect of the tumor or perioperative consequences leading to severe hypernatremic dehydration. Even in expert hands, management of water balance, in the absence of thirst is extremely challenging.

Case Description:

A 25-year-old gentleman, an electrician presented to the neurosurgical casualty with worsening headaches, impaired vision, and features of raised intracranial pressure over 2 months. He was found to have a large cystic suprasellar mass with well-defined margins measuring 2.7cm x 2.7cm x 3cm with chiasmal compression, suggestive of craniopharyngioma, complicating with bitemporal hemianopia, hypogonadotropic hypogonadism (LH 0.78IU/L, FSH 1.2IU/L, Testosterone 33ng/dL), secondary hypothyroidism, cranial diabetes insipidus, prediabetes sparing the cortisol axis. He underwent transcranial resection of the tumor, revealing WHO grade1 adamantinomatous craniopharyngioma followed by radiotherapy. The post-operative period was complicated with severe hypernatremia despite escalating doses and changing dosage forms of desmopressin from parenteral to nasal spray to oral tablets. Two weeks following discharge, he presented with severe hypernatremia (176mEq/L), polyuria, weight loss, hypotension, and altered sensorium where his lack of thirst was appreciated.

Conclusions:

In those with ADI, for the management of water balance, a "personalized approach" with the involvement of both patient and family is of paramount importance. With appropriate dose titration of desmopressin, careful fluid prescription, and frequent monitoring of electrolytes even at best centers, it is a battle that is hard to win.

Keywords: Adipsic Diabetes Insipidus, Craniopharyngioma, Hypernatremia

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Introduction

The normal water balance in the body is maintained by two critical mechanisms; secretion of arginine vasopressin (AVP) and thirst, in response to changes in the serum osmolality which is kept within a narrow range of 285-295mOsm/kg. AVP is secreted by the neurons situated in the supraoptic and paraventricular nuclei of the hypothalamus, packaged, and transported to the posterior pituitarywithin the axonal extensions where it is kept stored until a stimulus is received for release. Osmoreceptors are located in the organum vasculosum of the lamina terminals and in the parts of the anterior hypothalamus in close proximity to the above. Apart from the changes in osmolality, regulatory input from baroreceptors sensing the alterations in volume and pressure are important for

water homeostasis. In health, rising osmolality stimulates both release of AVP and thirst at a set threshold unique for each individual [1].

Central Diabetes Insipidus (CDI) is said to occur when there is no or minimal AVP release in response to rising osmolality resulting in hypotonic polyuria. Fairly uncommon (with a prevalence of 1/25000) in the general population, CDI is frequently encountered in certain conditions such as traumatic brain injury (TBI), craniopharyngioma, germinoma, granulomatous processes, and following pituitary surgery. The majority of patients with CDI have intact thirst which is vital to maintain eunatremia by generating water intake in response to polyuria. A combination of CDI with an absence of thirst is much rare and limited to nearly 100 cases reported in the literature, due to the damage that occurred in the areas of the anterior hypothalamus where osmoreceptors are located. ADI carries high morbidity and mortality, leads to recurrent hospital admissions and loss of thirst in most cases is permanent. As a consequence of hypernatremia or damage to the vital portions of the anterior hypothalamus, ADI is frequently associated with a higher incidence of venous thromboembolism (VTE), infections requiring hospital admissions, sleep aponea and central aponea, obesity, acute kidney injury, seizures and rhabdomyolysis [1-3].

Adipsia can be identified when there is an absence of thirst, in the setting of hypernatremia (>150mEq/L) and hyperosmolality (>310mOsm/kg) leading to a lack of spontaneous drinking. Especially in the postoperative setting, formal water deprivation tests are not necessary for objective diagnosis of ADI, and in the presence of severe hypernatremia and clinical instability, it is dangerous to follow the investigational protocols. Subnormal thirst response to hypertonic saline using a 10cm visual analog scale (VAS) can be used to diagnose ADI objectively, where patients are requested to point out their baseline thirst level (on a 0-10 scale) and then modify the level of thirst as the test proceeds with hypertonic saline infusion. Moreover, the amount of water consumed during the test can also help identify patients with disordered thirst. Interesting to note that, even though these patients lack the AVP response to hyperosmolality, they can retain the responsiveness to other stimuli such as hypotension through the baroreceptor pathway [1,4,5].

ADI has been reported first in literature following neurosurgical clipping of anterior communicating artery (ACOM) aneurysms with subarachnoid hemorrhage (SAH) as a result of infarction of the anterior hypothalamus perfused by the perforating branches of the ACOM. Furthermore, ADI is recognized in the setting of extensive surgery for large suprasellar tumors such as craniopharyngioma, germinoma, and pinealoma (Table 01). Craniopharyngioma is associated with an overall higher rate of CDI with intact thirst post-operatively (81-96%) while a reported rate of 7.1% for ADI is present. In the case series of post-surgical follow-ups of craniopharyngioma, tumor size >3.5cm and the presence of hydrocephalus pre-operatively were positively associated with the development of ADI whereas radiotherapy had no influence. ADI also appeared to have a slight male preponderance and was common among those in the second decade (median age at diagnosis of 17.5 years) [1,6,7].

Here, we describe a case of ADI following the resection of a large craniopharyngioma and provide a brief review of the literature on the management of ADI.

Case Presentation

brief review of the literature on the management of ADI.A 25-year-old gentleman, an electrician presented to the neurosurgical casualty with worsening headaches, impaired vision, and features of raised intracranial pressure over 2 months. Initial non-contrast computed tomography (NCCT) revealed cerebral oedema with hydrocephalus due to a mass lesion around 3rd ventricle suggestive of a colloid cyst (Figure 2), requiring urgent decompression via a ventriculoperitoneal (VP) shunt. He underwent an MRI brain with pituitary protocol revealing a cystic suprasellar mass with well-defined margins measuring 2.7cm x 2.7cm x 3cm in size with chiasmal compression, suggestive of a craniopharyngioma (Figure 2). He was referred to diabetes and endocrine unit of the National Hospital of Sri Lanka for further evaluation prior to definitive surgery.

Upon inquiry, he revealed a history of chronic persistent headaches for the past three years duration disturbing his daily activities. Surprisingly, he had brain imaging at the onset of these headaches revealing obstructive hydrocephalus at the 3rd ventricular level, which was overlooked and unevaluated for exotic reasons (Figure 1). The current presentation was precipitated due to progressive worsening of vision and severity of headaches, although he denied any features of hypothyroidism, or hypoadrenalism but claimed to have polyuria and polydipsia; requiring nearly 4 to 5L of fluid intake per day. He was single and sexually inactive and denied any loss of libido, or erectile dysfunction to suggest

hypogonadism.

On examination, he was averagely built with a BMI of 24.9kg/m2, well hydrated, had clean smooth pale skin, reduced hair in androgenic distribution and beard, bilateral gynecomastia along with an unremarkable cardiovascular, respiratory, and abdominal examination. At the bedside assessment of visual fields, a bitemporal hemianopia was noted which was confirmed later by perimetry (Figure 3). His pre-operative workup revealed hypogonadotropic hypogonadism, secondary hypothyroidism, cranial diabetes insipidus, prediabetes, and dyslipidemia (Table 2).

Following appropriate pre-operative optimization, he underwent right-sided craniotomy with complete excision of the tumor, histologically confirming WHO grade1 adamantinomatous craniopharyngioma. The post-operative period was complicated with wide fluctuations of sodium levels, and polyuria (>5mL/kg/hr), requiring frequent dose alterations of Desmopressin and targeted fluid management with free water and intravenous fluid therapy. He developed hyponatremia on postoperative day 10 lasting for 3 days, followed by permanent settling of diabetes insipidus. Furthermore, he required re-admission to the ICU with a deteriorating level of consciousness following the development of extradural hemorrhage at the surgical site (Figure 3), post-operative high fever with sepsis needing parenteral antibiotics, stress-induced hyperglycemia worsened by intravenous dexamethasone therapy requiring insulin infusion, lengthening his hospital stay for three weeks.

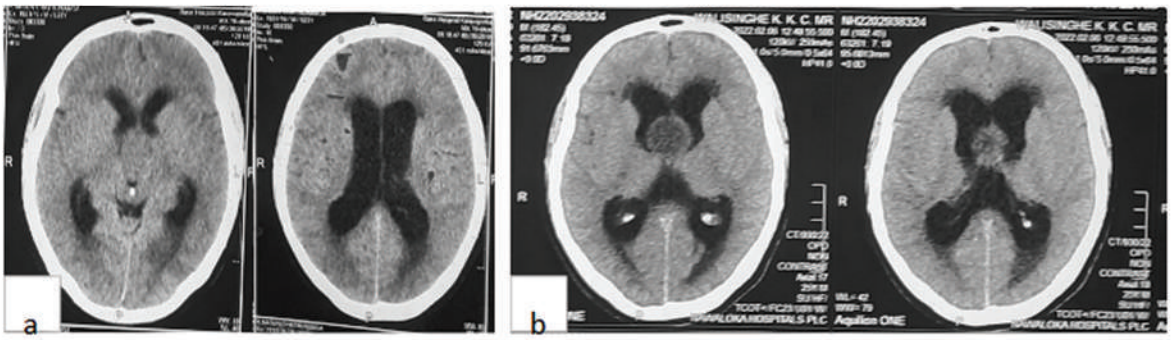

Figure 1: NCCT brain of the index patient showing marked hydrocephalus with obstruction at the 3rd ventricular level and a possible cystic mass lesion suggestive of a colloid cyst 3yrs before the current presentation, (b) at the current presentation

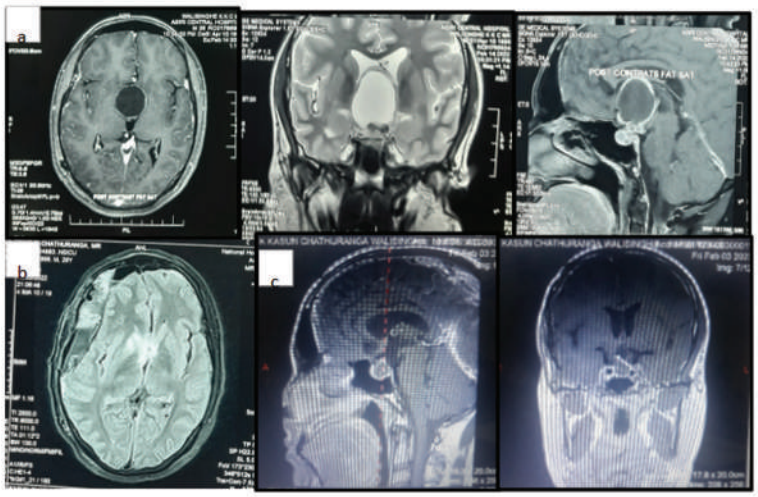

Figure 2: MRI brain with the pituitary protocol of the index patient
Pre-operative MRI- cystic suprasellar mass with well-defined margins (3.3x3.7x2.7cm) and mild wall enhancement with contrast, enlarged pituitary gland with chronic hemorrhagic foci, compression of the 3rd ventricle and VP shunt in situ
post-operative 2 weeks- R/acute extradural hematoma with midline shift, post-surgical changes
post-operative 1yr- no recurrence of the tumor, non-enhancing lesion in the pituitary fossa and suprasellar cistern indicating a residual post-surgical hematoma

Table 1: Causes of ADI[1]

Common causes	Uncommon causes
Craniopharyngioma (13-30%)	Neurosarcoidosis
ACOM aneurysm rupture/clipping (14-30%)	Macroprolactinoma
Congenital (5-20%) - Encephalocele - Holoprosencephaly - Agenesis of septum pellucidum - Dysgenesis of corpus callosum -Septo-optic dysplasia	Traumatic brain injury (TBI) Nonfunctioning pituitary tumor Cavernous hemangioma Germinoma Pinealoma Pseudotumor cerebri Langerhans cell histiocytosis CMV encephalitis Bacterial meningitis Toluene exposure

Table 2: Laboratory workup before surgery

Parameter	Patient's value	Reference range
Serum Creatinine	0.93 mg/dL	0.6 – 1.2 mg/dL
Serum sodium	148 mmol/L	135 – 148 mmol/L
Serum potassium	3.7 mmol/L	3.5 – 5.2 mmol/L
Serum osmolality	302 mOsm/kg	275-295 mOsm/kg
Urine osmolality	221 mOsm/kg	50-1200 mOsm/kg
Fasting Blood Sugar	115 mg/dL	65-100 mg/dL
HbA1C	6.3%	<5.6%
Lipid profile		
TC	252 mg/dl	<200 mg/dl
LDL	158 mg/dl	<130 mg/dl
HDL	39 mg/dl	<60 mg/dl
TG	105 mg/dl	<150 mg/dl
TSH	1.02 mIU/L	0.4 – 4.1 mIU/L
FT4	0.66 ng/dL	0.7-2.0 ng/dL
9am cortisol	314 nmol/L	nmol/L
LH	0.78 IU/L	1.8-8.6 IU/L
FSH	1.2 IU/L	1.5-12.4 IU/L
Total testosterone	33 ng/dL	241-827 ng/dL

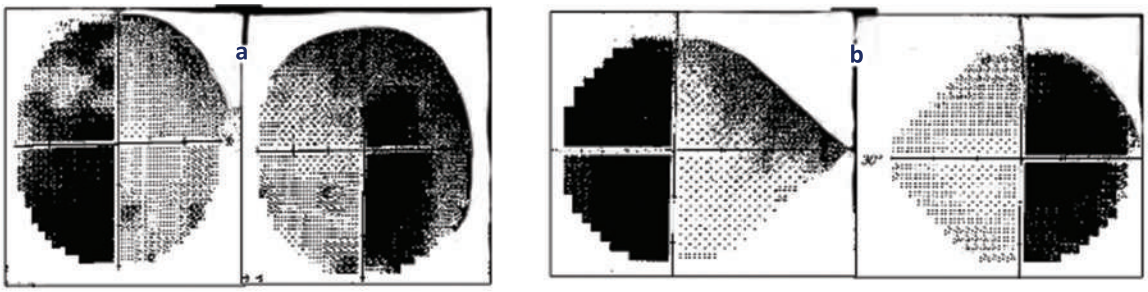

Figure 3: Visual perimetry showing bitemporal hemianopia (a) before surgery, (b) post-operative 8months

He was discharged on Thyroxine 75µg, Hydrocortisone 20mg daily in three divided doses, monthly IM Testosterone 250mg, Desmopressin nasal spray 2 puff nocte (20µg), Metformin 500mg twice daily and Sitagliptin 100mg mane for hyperglycemia. Two weeks following discharge, he presented with severe hypernatremia (176mEq/L), polyuria, weight loss, hypotension, and altered sensorium. Despite careful dose adjustments, fluid therapy, and the change of desmopressin dosage forms from parenteral to oral to intra-nasal therapy, the sodium could not be controlled. Upon inquiry, he denied polydipsia despite polyuria (>4ml/kg/d), hypernatremia (sodium 166mEq/L), and hyperosmolality (348mOs/kg) suggesting the possibility of ADI. His level of thirst on a VAS is shown (Figure 4). A thorough education of the patient and family, a water prescription per day, and escalation of oral desmopressin carefully to 200µg thrice a day, targeting a urine out-put of 1-1.5L/day and sodium in the upper-normal range, resulted in a good recovery; however, with frequent fluctuations (Figure 5).

At 3 months postoperatively, he received radiotherapy for residual disease while being maintained on hormonal replacement therapy. He has left with permanent bitemporal hemianopia (Figure 3), requiring shifting to light duty, and is currently under close surveillance for fluctuation of sodium levels. Post-operative one-year neuroimaging was satisfactory with no recurrence tumor except for a residual hematoma (Figure 2).

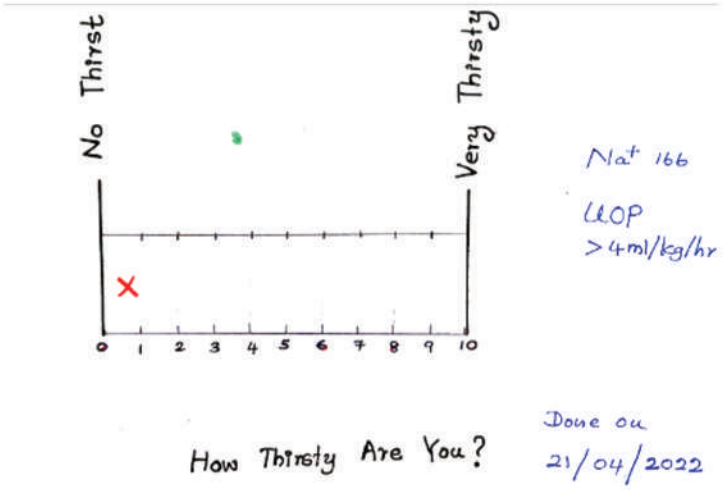

Figure 4: VAS of the index patient showing minimal or no thirst in the presence of hypernatremia

Discussion

This case illustrates a typical presentation of ADI following the excision of a large craniopharyngioma where there was hypernatremia with increased osmolality in the presence of large volumes of inappropriately diluted urine and low or minimal thirst. Our patient also went through the typical triphasic phasic response of initial diabetes insipidus (DI) followed by the syndrome of inappropriate ADH secretion (SIADH) and finally left behind with a permanent DI. The first phase of transient DI occurs due to a partial or complete pituitary stalk section which disconnects the hypothalamic osmoregulatory centers from the posterior pituitary preventing the release of stored AVP within 24hrs to 5 days postoperatively. Then the SIADH occurs due to the unregulated release of AVP from degenerating axonal endings in the posterior pituitary following surgical stress within 6 days to 11 days postoperatively. Finally, the permanent DI settles in when all AVP stored are depleted and nearly 80-90% of AVP-secreting neuronal cell bodies in the hypothalamus have undergone degeneration as a consequence of intra-operative damage. This characteristic triphasic response is seen (a diuretic-anti diuretic and another diuretic phase) in about 1.1%-3.4% of cases [2].

Management of ADI is complex, based on expert opinion, and involves the maintenance of eunatremia, minimizing polyuria and sleep disruption. However, even with strict monitoring, record keeping, good adherence to desmopressin, smooth control of water homeostasis, and sodium balance is far from reality in the absence of thirst. Both oral and intranasal Desmopressin have beenused with success without one being superior to the other. The basic rule is to have fixed dosing of Desmopressin to achieve a daily urine output of 1.5 and 2 L (the volume which is equivalent to the obligate daily intake in most temperate climates) and alter the water prescription according to the weight changes. Target weight is taken as the weight when the patient is euvolemic and eunatremic. Weight gain is tackled by reducing the water intake and weight loss is by increasing the water intake on a 1kg= 1L basis. Frequent assessments are paramount to avoid wide fluctuations in osmolality and sodium levels as numerous day-today-activities and encounters such as intercurrent illnesses, exercise, and temperature differences can contribute to changes in the insensible loss [1].

There have not been any significant differences among the effectiveness of different administration routes of desmopressin although intra nasal route is not reliable in patients with cognitive impairment as the inhalation of the spray will not be optimal. Sublingual desmopressin has shown greater bioavailability (>60%) compared to oral desmopressin tablets although not as parenteral therapy. Concomitant ingestion of food can interfere with absorption; hence meals should be avoided 1hr before and after sublingual desmopressin [8-11]. In Sri Lankan setup is available for us is the intranasal spray and the oral tablets. We used both forms in our patient depending on the availability and affordability of the patient without significant differences in efficacy between them.

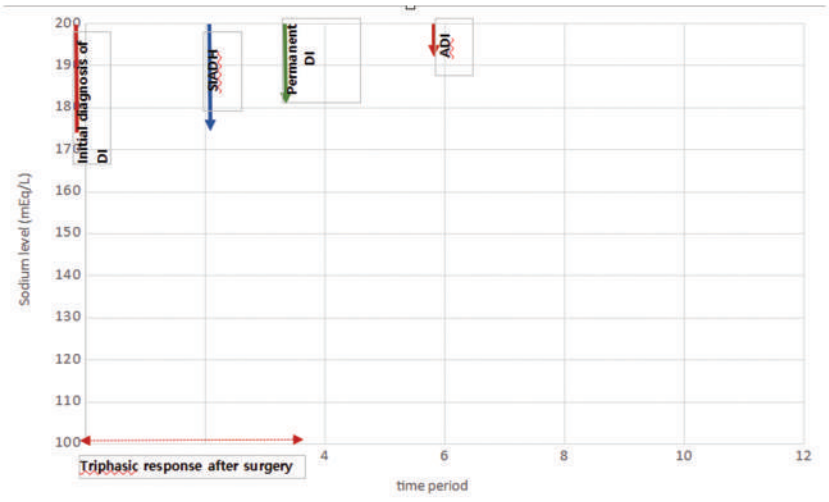

Figure 5: Fluctuation of sodium levels during the follow-up

In addition to the above, Chlorpropamide (250-500 mg orally daily), a first-generation sulphonylurea has been reported in the literature as an effective therapeutic option to restore normal drinking behavior independent of its renal effects. Although, hypoglycemia, skin rashes, liver injury, and hematological abnormalities are reported as possible undesired effects of Chlorpropamide [12,13]. For our patient, we could not consider Chlorpropamide due to its unavailability and undesirable side effects.

How frequently we need to monitor serum sodium is a question that is unanswered due to the lack of scientific data from studies considering the rarity of the disease. A pillar of success in outpatient care for patients with ADI is close monitoring as both high and low levels of sodium can complicate follow-up care [14]. Weekly serum electrolytes have been suggested as there are no portable analyzers for home monitoring of sodium as in the case of blood glucose in diabetes mellitus (DM). In our patient, hence he had good intelligence and good family support, even though he resides far away from our hospital, we could monitor his sodium levels once in two weeks and communicate the reports through WhatsApp media to make the necessary adjustments in fluid prescription and desmopressin doses.

The biggest challenge for the patient and the family is to keep the track of water intake and remember to drink especially when he is at work. He was asked to have a reminder system on his smartphone and keep a record of fluid intake in it so that he can transfer the data to a water diary when he is at home. Despite all of the above interventions still, his sodium level maintains at 145 to 150mEq/L and at times shoots up until 155mEq/L.

Once ADI sets in permanent loss of thirst is the rule. However, as exceptions to the rule, 3 cases have been reported in the literature with the regaining of the thirst response although without recovery of AVP secretion to hyperosmolality. All these patients were young children following craniopharyngioma surgery and had an average of 6.7 months to recover possibly due to neuronal plasticity in the areas of the thirst center [15]. Hence, it is important to re-visit the diagnosis of ADI esp. in the case of a young child with this disorder.

Conclusion

ADI is an extremely rare complication of hypothalamic disorders occurring as a result of disruption of the thirst center leading to loss of hierarchical control of serum osmolality and AVP release. Patients suffering from ADI should be carefully managed with dose alterations of Desmopressin, fluid balance, and patient and family education. Despite personalized care approaches and close monitoring of serum sodium levels, it is still impossible to mimic the round-the-clock quasi-physiological osmoregulation of the human brain.

Consent

Consent was given by the patient for this case report.

Conflicts of interests

The authors have no conflict of interest to declare.

Abbreviations

ACOM	Anterior Communicating Artery
ADI	Adipsic Diabetes Insipidus
AVP	Arginine vasopressin
CDI	Central Diabetes Insipidus
CMV	Cytomegalovirus
DI	Diabetes Insipidus
DM	Diabetes Mellitus
FSH	Follicular Stimulating Hormone
ICU	Intensive Care Unit
IM	Intramuscular
LH	Luteinizing Hormone
NCCT	Non-Contrast Computed Tomography
NDI	Nephrogenic Diabetes Insipidus
PP	Primary Polydipsia
SAH	Subarachnoid Hemorrhage
SIADH	Syndrome of Inappropriate ADH Secretion
TBI	Traumatic Brain Injury
VAS	Visual Analog Scale
VTE	Venous Thromboembolism

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