Clinical Approach to Sodium Homeostasis Disorders in Children with Pituitary-Suprasellar Tumors

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Keywords

Hyponatremia · Hypernatremia · Pituitary tumors · Children

Abstract

Children with pituitary-suprasellar tumors are at high risk of developing sodium metabolism disorders since the tumoral mass itself or surgical and medical treatment can damage AVP release circuits. Additional risk factors are represented by the use of hypotonic fluids, the young age, total parenteral nutrition, and obstructive hydrocephalus secondary to tumor pathology. The most frequent hyponatremic disorders related to AVP in these patients are the syndrome of inappropriate ADH secretion and the cerebral/renal salt wasting syndrome, while hypernatremic conditions include central diabetes insipidus (CDI) and adipsic CDI. The main challenge in the management of these patients is to promptly distinguish the AVP release disorder at the base of the sodium imbalance and treat it correctly by avoiding rapid sodium fluctuations. These disorders can coexist or follow each other in a few hours or days; therefore, careful clinical and biochemical monitoring is necessary, especially during surgery, the use of chemotherapeutic agents, or radiotherapy. This monitoring should be performed by experienced healthcare professionals and should be multidisciplinary, including pediatric endocrinologists, neurosurgeons, and

oncologists since maintaining sodium homeostasis also plays a prognostic role in terms of disease survival, therapeutic response, hospitalization rate, and mortality. In this review, we analyze the management of sodium homeostasis disorders in children with pituitary-suprasellar tumors and discuss the main challenges in the diagnosis and treatment of these conditions based on literature data and over 30 years of clinical experience at our Department of Pediatric Endocrinology.

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Introduction

The sodium and water balance is regulated by many hormonal and neuronal circuits that cooperate for the maintenance of serum sodium and osmolality within the normal ranges [1–7]. This strict regulation explains the fact that imbalance of sodium homeostasis is the most common electrolyte alteration in hospitalized children [8, 9]. Sodium is the main electrolyte in extracellular fluids, and it is fundamental for the well-being of many tissues, especially for neurons and for growth plate cartilage; its derangements influence neuro-psychomotor development and growth in very young patients [10–13]. Rapid fluctuations in serum sodium lev-

els are associated with symptoms that vary depending on the severity of the hypo- or hypernatremia, ranging from asymptomatic states to failure to thrive, anorexia, nausea, vomiting, headache, seizures, irritability, confusion, hallucinations, seizures, coma, and even death. In patients with hypothalamic-pituitary lesions, the cerebral tumor mass damages the neuroanatomical circuits of AVP release and exposes these children to disorders of sodium metabolism in a higher ratio than pediatric patients with blood tumors, solid non-brain solid tumors, or also other cerebral tumors that do not affect the pituitary region (e.g., medulloblastoma or ependymoma). On the other hand, the medical/surgical treatment of hypothalamic-pituitary tumors increases the risk of developing sodium metabolism disorders influencing AVP release. The most frequent tumor masses in the pituitary-suprasellar region are craniopharyngioma (5–15%), ganglioglioma (10–18%), and germinoma (3%), which represent about 19% of all brain tumors in childhood, while pituitary adenomas are uncommon at this age [13–19]. Pediatric patients with these types of tumors are at high risk of hyponatremia and hypernatremia at any time, before the tumor is diagnosed, during and after neurosurgery, during chemotherapy or radiotherapy and in case of recurrence of the disease [14–20]. The main risk factors are age-related, that is, the younger the patient, the more frequent and severe the hyponatremia or hypernatremia, but also linked to the tumor site, more frequent in case of pituitary and stalk involvement, to neurosurgery of the pituitary or of the suprasellar area, to the neuroanatomical integrity of the thirst circuits, to the type of chemotherapy drugs, if vincristine, cyclophosphamide, carbamazepine, opioids, methotrexate, and even to the hypotonic fluids usually prescribed during chemotherapy and radiotherapy. Moreover, the often associated nausea promotes the secretion of AVP, leading to a hyponatremic state further worsened by the vomiting. Obstructive hydrocephalus and total parenteral nutrition are other risk factors that can contribute to the development of an imbalance of sodium metabolism [21–31].

In children with parasellar tumors, the syndrome of inappropriate ADH secretion (SIADH) and the cerebral/renal salt wasting syndrome (C/RSW) represent the most frequent hyponatremic disorders [32–40], while central diabetes insipidus (CDI) and the adipsic CDI are the main hypernatremic ones [14, 20, 41–51]. These conditions can coexist in the same patient or follow each other in a few hours or days, so close clinical and biochemical monitoring is mandatory [52–61].

These conditions can be acute or chronic, transient, or persistent and may be associated with any hormonal deficiency of the anterior pituitary (ACTH, TSH, GH, or LH/FSH deficiency), hypothalamic obesity, or more rarely a precocious puberty, gonadotropin-dependent or induced by β -human chorionic gonadotropin secretion.

Because hyponatremia and hypernatremia can be associated with severe neurological symptoms and cellular damage, timely diagnosis and treatment are essential to avoid related sequelae. Recent literature data indicate that the maintenance of sodium homeostasis has a prognostic role in terms of disease survival, therapeutic response, hospitalization rate, and even mortality [10–13].

A novelty in the diagnosis of sodium imbalances is the introduction of the copeptin measurement, an AVP surrogate, secreted in an equimolar way, especially useful in the case of hyponatremia.

Similarly, as regards the treatment of pituitary tumors and endocrine sequelae, a great improvement over the years is linked to the greater knowledge of neuroanatomical structures and to their rescue during surgery, to the revision of chemotherapeutic protocols, to the use of new radiotherapeutic strategies with proton beams, to the replacement of hypotonic infusions with isotonic fluids as maintenance liquids during chemotherapy, and to the introduction of new classes of drugs, such as vaptans, in the treatment of chronic SIADH.

However, sodium metabolism disorders are still common in these patients, and management is still challenging with the need for a multidisciplinary approach that includes pediatric endocrinologists, neurosurgeons, and oncologists.

The purpose of this paper is to review the diagnostic and therapeutic management of sodium homeostasis disorders in children affected by pituitary-suprasellar tumors, based on literature data and over 30 years of clinical experience in our Pediatric Endocrinology Department in which we took care of over 100 patients with pituitary-suprasellar tumors, of which 21 with germinomas, 43 with craniopharyngiomas, and 41 with astrocytomas, almost all experiencing derangements of sodium metabolism during the follow-up period.

Hyponatremia Clinical Management

Definition

Hyponatremia is defined by serum sodium levels below 135 mmol/L; it can occur in case of sodium net loss or volume overload. In relation to the volumic state, hyponatremia may be euvolemic, hypovolemic, or hyper-

Fig. 1. The clinical management of hyponatremia.

volemic, whereas by considering the severity it can be classified as mild (134–130 mmol/L), moderate (129–124 mmol/L), and severe (<124 mmol/L).

Clinical and Biochemical Evaluation

The clinical management of hyponatremia is represented in Figure 1.

In front of a condition of hyponatremia, the urinary production and the sodium content of intravenous fluids possibly administered, as well as the quantities of liquids orally ingested, must be precisely quantified; any drug that interferes with serum sodium levels should also be considered. At first, in the presence of hyponatremia the

evaluation of the thyroid and adrenal function is of primary importance to exclude hypothyroidism or hypocortisolism, a frequent cause of hyponatremia, and, if present, must be corrected. Further biochemical evaluations should include blood counts, serum potassium, creatinine, urea, osmolality and copeptin values, urine density and osmolality, and sodium excretion.

Clinical Management of the Main Hyponatremic Conditions

Hypothyroidism or Hypocortisolism

Primary or secondary hypothyroidism or hypocortisolism may occur in patients affected by brain tumors due

to hypothalamic/pituitary surgical or radiation injury or chemotherapy agents [52, 62–65]. Radiation doses above 20 Gy are related to the development of central hypothyroidism; when the dose is above 30 Gy the risk is higher for both central and primary hypothyroidism. The use of chemotherapeutic agents such as lomustine, bleomycin, and cyclophosphamide has also been related to the hypothalamic-pituitary-thyroid axis (HPTA), although the estimated risk attributable to chemotherapy is much lower than that for radiotherapy, which is inversely associated with age at exposure. Compared to other pituitary hormone axes, the dysfunction of the hypothalamic-pituitary-adrenal axis (HPAA) is more resistant to cranial irradiation, but in case of an irradiating dose above 30 Gy, the risk of injury increases. In the absence of intracranial or total body irradiation, chemotherapy-related HPAA dysfunction is uncommon. Adrenal insufficiency related to chemotherapy may be present in acute treatment, but the evidence of its long-term effects is minimal. Iatrogenic adrenal insufficiency is common in children with brain tumors after prolonged high doses of glucocorticoid therapy and may persist for some time even if treatment is gradually discontinued. Therefore, thyroid and adrenal function has to be evaluated periodically, generally every year, and in the case of indicative symptoms, such as fatigue, reduced resistance, poor weight gain, which however are very nonspecific and common in children with cancer, and in the case of hyponatremia or hypoglycemia. Evaluation of thyroid function includes TSH, fT4, fT3 dosage, titration of anti-thyroid-peroxidase and thyroglobulin antibodies, and ultrasound control of the thyroid gland. The biochemical investigation of HPAA is more difficult to assess because morning cortisol and ACTH evaluation or cortisol profile may not be sufficient at all, and dynamic tests such as the ACTH test with low dose (1 µg i.v.) or standard dose (250 µg i.v.) and an insulin tolerance test may be required. In case of HPTA or HPAA, replacement treatment should be started as soon as possible with L-thyroxine (1–4 µg/kg/day) and/or hydrocortisone (10 mg/m²/day) [62, 63].

Syndrome of Inappropriate ADH Secretion

SIADH is a condition of euvoletic hyponatremia [66]. The typical presentation includes hyponatremia (<135 mmol/L), low serum osmolality (<275 mOsm/kg), inappropriately high urine osmolality (>100 mOsm/kg), and euvoletic with contraction of diuresis and lowered osmotic threshold for thirst. Usually, there are no symptoms of water retention, since normally only a third of the body water content is found in the extracellular compart-

ment. SIADH is mainly a chronic condition, but in oncologic patients it is often an acute and dramatic event, difficult to manage.

The treatment of chronic hyponatremia due to SIADH requires fluid restriction (20 mL/kg/24 h or about 500 mL less than daily urinary output), while the treatment of acute and severe symptomatic hyponatremia may require intravenous sodium supplementation through iso-hypertonic solutions [66–77]. Obtaining or maintaining fluid restriction is often a challenge due to the poor compliance of these subjects who have a lower thirst threshold [75]. In our experience, the restriction of fluids is often difficult to obtain even for the concomitant use of other therapeutic agents, such as antibiotics or chemotherapy drugs needing larger amounts of fluids, or due to the high proportion of fluids administered to preserve kidney function. In these cases, oral sodium supplementation (1–2 g/day) may also be necessary. When the underlying disease responsible for the SIADH is a chronic condition, that is, linked to a large tumor mass in the suprasellar region, chronic hyponatremia can occur, with potential severe neurological symptoms such as seizures and consciousness alteration. This complication can drive the decision to use a class of drugs called vaptans, aquaretic agents capable of inducing polyuria [78–82]. For this treatment, children must be hospitalized, and they must start with low-dose titration; subsequently, the dosage should be modulated by monitoring serum sodium levels and urine output for at least 48–72 h. To avoid a rapid fluctuation of the serum sodium level, patients can have free access to water during this therapeutic regimen, but they must be strictly monitored for changes in sodium and osmolality, and the previous treatments of hyponatremia must be progressively withdrawn.

Usually, serum sodium normalizes in 24–48 h, while urinary output stabilizes in 15–20 days, due to the electrolyte-free aquaresis caused by tolvaptan. However, so far few studies have been published on the use of tolvaptan in pediatric age and for patients under the age of 18, both in Europe and in the USA, and today it is still considered an off-label drug. Although current data indicate good efficacy and safety, to reinforce these preliminary results on its use in euvoletic hyponatremia related to SIADH in children, further studies are needed [78–82].

Cerebral/Renal Salt Wasting Syndrome

The cerebral salt wasting (CSW) syndrome, more correctly defined as C/RSW, is an acute hypovolemic hyponatremic condition whose pathogenetic mechanism is

Table 1. Main clinical and biochemical differences between SIADH and C/RSW

	SIADH	C/RSW	Reference
Body weight	increased	stable or decreased	[13, 83]
Arterial blood pressure	stable or increased	decreased	[13, 83]
Dehydration	no	yes	[13, 83]
Serum sodium	decreased	decreased	[13, 83]
Urine sodium	increased	increased	[13, 83]
Urine output	decreased	increased	[13, 83]
Serum osmolality	decreased	decreased	[13, 83]
Urine osmolality	increased	increased	[13, 83]
Urine osmolality/ serum osmolality	>1	>1	[13, 83]
Serum urea	decreased	normal/increased	[13, 83]
Serum urate	decreased	increased	[13, 83]
Hematocrit	decreased	normal/increased	[13, 83]
Serum ADH	increased	first decreased and then increased (but lower than in SIADH)	[13, 83], modified
Serum copeptin	increased	first decreased and then increased (but lower than in SIADH)	[13, 83], modified
Serum natriuretic peptide	increased	increased	[13, 83]
Serum copeptin/ urinary sodium ratio	<0.3	>0.3	[84]

still controversial. It seems to be related to a reduction of renal sympathetic stimulation, with a concomitant involvement also of natriuretic peptides in the brain, resulting in a suppression of renin, aldosterone, and AVP secretion [13, 35–39]; the final result is renal sodium reabsorption decrease, with consequent hypovolemic state.

In C/RSW, the hypovolemic stimulus is more effective on AVP secretion than the hypo-osmolar one; the subsequent compensatory AVP release is then responsible for the hyponatremic state despite the low serum osmolality. Typical features of this condition are hyponatremia, hypovolemia, and renal sodium loss resulting in an increase in urine output and high urine osmolality. In some cases, it is very challenging to distinguish C/RWS from SIADH, as the volemic state is the only marker that allows the definite diagnosis; hypovolemia is present in the C/RSW, whereas euvoemia is typical of the SIADH condition. The main clinical and biochemical features of SIADH and C/RSW are represented in Table 1.

The C/RSW treatment requires the integration of liquids and salt to support circulation and compensate for renal sodium loss [13, 15]. The daily sodium supplement is shown in Table 2; the daily fluid requirement is higher than the norm, equal to 80–100 mL/kg/day. When hyponatremia persists, fludrocortisone at 0.025–1 mg/day can be used.

Rapid correction of serum sodium must be avoided; the standard sodium correction over time should be 4–6 mmol/L in the first 4–6 h, 10–12 mmol/L in the first 24 h, <18 mmol/L in the first 48 h [13].

Hyponatremia Related to Hypotonic Fluids and Drugs

To avoid the imbalance of sodium and water homeostasis and to promptly adjust the 1-deamino-8-D-arginine-vasopressin (d-DDAVP) dosage in CDI patients, during chemotherapy or radiotherapy, serum sodium and osmolality, urinary osmolality, and output must be carefully monitored.

The high rate of hypotonic fluid maintenance, the use of potential ADH-like drugs, such as vincristine, vinblastine, ifosfamide, and cisplatin, and SIADH induced by nausea/vomiting are the main risk factors of development of hyponatremia during chemotherapy; the inflammatory state of the neuronal tissue and/or the change in the volume of the tumor mass can lead to C/RSW in exceptional cases during radiotherapy [65].

Indeed, during chemotherapy, large amounts of fluids are needed to preserve kidney function and avoid the toxicity of chemotherapy drugs; however, hypotonic fluids should be avoided in patients in pediatric age with brain tumors, especially when the neuroanatomical circuits of thirst and the release of AVP release are compromised.

Fig. 2. The clinical management of hypernatremia.

Table 2. Daily sodium intake in relation to hyponatremia

Serum sodium	Sodium daily administration, mmol/L/kg/day
130–135 mmol/L	2–3
124–130 mmol/L	5–6
<124 mmol/L	6–10

From our own experience, also supported by data from the literature, in that situation the standard maintenance fluids are represented by isotonic solutions [83–88].

In patients with CDI and concomitant SIADH, fluid restriction is needed, and d-DDAVP dosage reduction or temporary withdrawal is indicated; in case of C/RSW, the main challenge is to interpret the worsening of polyuria, by differentiating between an insufficient d-DDAVP dosage from coexistence of the CDI and C/RSW conditions [13, 89]. Low urine sodium and low urine osmolality should help in orienting towards a d-DDAVP dose in-

crease; high urine sodium and high urine osmolality should drive the decision to administer fluids and sodium and eventually reduce the d-DDAVP dosage.

Hypernatremia Clinical Management

Definition

Hypernatremia is defined by serum sodium levels above 145 mmol/L and occurs in presence of sodium excess, pure water loss, or low fluid intake.

Clinical and Biochemical Evaluation

The clinical management of hypernatremia is represented in Figure 2. Urinary output and the sodium content of liquids possibly administered intravenously, as well as the amount of fluid ingested orally and the presence of a thirsty sensation must be precisely quantified. Any medication that interferes with serum sodium levels should also be considered. Further biochemical evaluation should include a serum sample for blood count, po-

tassium, creatinine, urea, osmolality, and copeptin and a urine sample for density, osmolality, and sodium.

Clinical Management of the Main Hypernatremic Conditions

Central Diabetes Insipidus

CDI is clinically characterized by polyuria-polydipsia with extremely diluted urine excretion, inability to concentrate urine due to AVP deficiency, and consequent compensatory polydipsia [13, 44, 45, 51, 90–94]. When the compensatory mechanism of polydipsia fails, dehydration, vomiting, fever, irritability, sleep disorders, and failure to thrive develop.

In the suspicion of CDI, the first investigations should foresee the evaluation of serum sodium, osmolality and copeptin levels and urine osmolality [13, 44, 45, 51, 92]. Serum sodium values >145 mmol/L, serum osmolality >300 mOsm/kg, and urinary osmolality <300 mOsm/kg are indicative of the condition [13, 44, 45, 51, 92]. Although the diagnosis of CDI usually requires a water deprivation test and desmopressin (DDAVP) to distinguish CDI from a nephrogenic diabetes insipidus or primary polydipsia, in patients with already diagnosed brain tumors the test is not necessary.

The tumor lesions of the pituitary region that most frequently cause CDI are germinomas, histiocytosis of Langerhans cells, and pinealoma [13]. Neurosurgical lesions of the pituitary stalk and/or of the neurohypophysis are other common causes of acquired CDI, especially when a large tumor in the sellar/suprasellar region is present, as in the case of gangliogliomas or craniopharyngiomas. The development of CDI depends mainly on the neurosurgical approach used, which may be transcranial or transsphenoidal, by the more conservative or rather highly destructive resection amplitude, and by radiotherapy; an approach aimed at saving the hypothalamus seems to have a protective role against the appearance of CDI [95–100].

CDI may be permanent, in case of neuronal loss of AVP-releasing cells, or transient, during neurosurgery or in the subsequent postoperative hours. In 3.4–22.5% of cases, a “triphasic” pattern may be present: in the first 24–48 h after the surgery, a transient CDI is present due to edema and pituitary stalk inflammation; subsequently, a phase lasting 1–10 days is characterized by necrosis of the neurohypophyseal cells and consequent release of AVP that causes SIADH; the third phase, which occurs when $>90\%$ of the neurohypophyseal function is lost, is characterized by a permanent CDI and occurs in 75–85% of patients undergoing sellar/suprasellar neurosurgery [13, 20, 46, 49].

Patients that have experienced the “triphasic” pattern usually develop permanent CDI [95–100]; therefore, neurosurgery is an important step in the treatment of pituitary/suprasellar tumors, and the management of sodium and fluids during the intra- and postoperative phase is quite challenging as both hypernatremia and hyponatremia can occur.

In children with preexisting CDI, d-DDAVP should be administered regularly 6–12 h before surgery, while in children without preexisting CDI, the measurement of copeptin may point towards the probability of developing CDI [101–104]. To avoid intraoperative water intoxication in patients with CDI, d-DDAVP treatment should be discontinued on the morning of surgery.

Regardless of the previous unbalanced sodium metabolism conditions, during neurosurgery the fluid infusion velocity and concentration are calculated based on serum sodium measurements, urine output, and urine osmolality recorded every hour; when serum sodium is >147 mmol/L and urine osmolality <300 mmol/kg H_2O , and urinary output >2.5 mL/kg/h for >2 h, d-DDAVP should be administered intravenously at a dose of 0.5–1 μ g in children aged <2 years or >2 years, respectively.

In the 24 h after surgery, serum sodium and osmolality, urinary osmolality, and output are measured and recorded every 4 h; hydroelectrolytic infusion is calculated as during the neurosurgery, and intravenous d-DDAVP is administered when necessary, until patients wake up and feel thirsty.

Furthermore, during the intra- and postoperative period of 24–48 h, continuous intravenous hydrocortisone at the dose of stress needs to be administered. When the clinical conditions allow oral ingestion, the hydroelectrolytic infusion must be progressively reduced, the oral fluid intake progressively increased, and any hormone replacement treatments for hypothyroidism, hypocortisolism, and CDI administered again [14].

To detect and treat late hyponatremia or the onset of transient/permanent diabetes insipidus, sodium and water metabolism should be evaluated up to 7–14 days after surgery [13, 20, 44, 45, 51, 92].

The treatment of permanent CDI consists of d-DDAVP, which can be administered orally, sublingually, intranasally, or intravenously [13, 54, 61, 90, 92]. Actually, the most used way for oral treatment is the sublingual formulation, with an initial dose of 1–4 μ g/kg/day in 2–3 administrations, starting with the lowest dose due to the high renal response, to increase it later, based on the signs of polyuria-polydipsia and serum sodium levels.

Adipsic CDI

Adipsic CDI is a particular form of CDI caused by lesions at the level of hypothalamic osmoreceptors, supra-optic/paraventricular or neurohypophyseal regions. Despite the increase in serum osmolality, patients do not feel thirsty and become hypernatremic and dehydrated. This condition is often associated with septo-optic dysplasia or with massive suprasellar cerebral tumors, especially after neurosurgical intervention.

To maintain eunatremia, the standard treatment is represented by d-DDAVP administration and frequent supply of liquids in relation to body weight (40 mL/kg + 300 mL/m² perspiration) [13].

Hypernatremia Related to Fluids and Drugs

To avoid iatrogenic hypernatremia, intravenously administered fluids should always be evaluated for sodium content and infusion rate; hypertonic solutions should be modified in isotonic fluids in relation to the volemic status and sodium correction rate [83–86].

Drug-related hypernatremia can occur when osmotic diuretics are administered. In children with prior CDI diagnosis, in case of persistent hypernatremia, d-DDAVP dosage has to be corrected.

Conclusions

Disorders of sodium homeostasis are the most frequent electrolytic alterations observed in pediatric cancer patients. Among these conditions, pituitary/suprasellar

tumors are at greater risk of developing such complications for lesions in the neuroanatomical circuits of thirst and AVP release.

The maintenance of sodium homeostasis is fundamental not only for neuro-psychomotor development, but also for a better response to treatment and for the disease survival rate. Only a close multidisciplinary cooperation between pediatric oncologists and pediatric endocrinologists allows the achievement of the best management in such severe and complex disorders.

Statement of Ethics

The authors have no ethical conflicts to declare.

Disclosure Statement

On behalf of all authors, the corresponding author declares no conflicts of interest.

Funding Sources

No grant or fellowship has supported this paper.

Author Contributions

Consent to submit has been explicitly received from all co-authors. All authors whose names appear in the submission have sufficiently contributed to the scientific work and therefore share the collective responsibility and accountability for the results.

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