Clinical approach to sodium homeostasis disorders in children with pituitary-suprasellar tumors

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Gerdi Tuli[1,2], Patrizia Matarazzo[1], Luisa de Sanctis[1,2]

[1]Department of Pediatric Endocrinology, Regina Margherita Children's Hospital, City of Health and Science University Hospital of Turin

[2]Department of Public Health and Pediatric Sciences, University of Turin.

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Corresponding author:

Dr. Gerdi Tuli

gtuli@unito.it

Piazza Polonia 94, 10126, Turin, Italy

+ 39 3493232854 ; + 39 0113135687

For reprint request:

Dr. Gerdi Tuli

Piazza Polonia 94, 10126, Turin, Italy

Ethical Statement:

The manuscript has not been submitted to more than one journal for simultaneous consideration and has not been published previously.

No data have been fabricated or manipulated (including images) to support our conclusions

No data, text, or theories by others are presented as if they were the author's own.

Consent to submit has been received explicitly from all co-authors.

All authors whose names appear on the submission have contributed sufficiently to the scientific work and therefore share collective responsibility and accountability for the results.

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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 smart regulation explains the fact that sodium homeostasis imbalance represents the commonest electrolyte alteration in hospitalized children [8-9]. Sodium is the main electrolyte in the extracellular fluids and it is fundamental for many tissues wellness, above of for neurons and for the growth plate cartilage; its derangements influence neuropsychomotor development and growth in very young patients [10-13]. Rapid fluctuations in sodium serum levels are associated with symptoms that vary in relation to hypo or hypernatremia severity, 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 harms the neuroanatomical circuits of AVP release and exposes these children to sodium metabolism derangement in higher ratio with respect to pediatric patients affected by blood cancer, solid non-cerebral tumors or even other cerebral tumors not affecting the pituitary region (e.g. medulloblastoma or ependimoma). On the other hand, the medical/surgical treatment enhances the risk to develop sodium metabolism disorders by influencing the AVP system release. The most frequent tumor masses of the pituitary-suprasellar region are craniopharyngioma, ganglioglyoma and germinoma, accounting for about 10% of all brain tumors in childhood [14]. Pediatric patients affected by these types of tumors are at high risk of hyponatremia and hypernatremia at any time, before tumor diagnosis, during and after neuro-surgery, during chemotherapy or radiotherapy and in case of disease relapse [13-15]. The major risk factors are related to the age, i.e. the younger is the patient the more frequent and severe is the hyponatremia or hypernatremia, to the tumor site, i.e. more frequent in case of pituitary and stalk involvement, to the neurosurgery of pituitary or suprasellar area, to the neuroanatomical integrity of thirst circuits, to the type of chemotherapy drugs, i.e. vincristine, cyclophosphamide, carbamazepine, opioids, methotrexate, and even to the hypotonic fluids usually prescribed during chemotherapy and radiotherapy. The often associated nausea promotes AVP secretion, leading to a hyponatremic state further worsened by the vomiting.

The syndrome of inappropriate ADH secretion (SIADH) and the cerebral/renal salt wasting syndrome (C/RSW) represent the most frequent hyponatremic disorders in oncologic pediatric patients [16-23]; conversely, central diabetes insipidus (CDI) and the adipsic CDI are the main hypernatremic ones [13,15,24].

These conditions can acutely or chronically occur, can be transient or persistent and may be associated with any hormonal deficiency from the anterior pituitary (ACTH, TSH, GH or LH/FSH

deficiency), hypothalamic obesity or more rarely with precocious puberty, gonadotropin-dependent or β-human Chorionic Gonadotropin (βhCG)-induced.

Since either hyponatremia and hypernatremia can be associated with severe neurological symptoms and cellular damage, a prompt diagnosis and treatment are fundamental to overcome the related sequelae. Recent literature data indicate that sodium homeostasis maintenance has a prognostic role in term of disease survival, therapeutic response, hospitalization rate and even mortality [10-13, 25, 26].

The aim of this paper is to review the management of sodium homeostasis disorders in children affected by pituitary-suprasellar tumors and to discuss about the main challenges in the diagnosis and treatment of these conditions on the basis of literature data and of over 30 years of clinical experience at our Pediatric Endocrinology Department.

HYPONATREMIA CLINICAL MANAGEMENT.

Definition.

Hyponatremia is defined by serum sodium below 135 mmol/L; it can occur in case of sodium net loss or volume overload. In relation to the volemic state hyponatremia may be euvolemic, hypovolemic or hypervolemic, 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. Urinary output and sodium content of eventually administered intravenous fluids, as well as orally ingested fluid amounts have to be accurately quantified; any drug interfering with serum sodium levels have to be considered as well. At first, evaluation of thyroid and adrenal dysfunction is needed to exclude hypothyroidism or hypocortisolism, and has to be corrected. Further biochemical evaluations should include blood count, 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 [24]. Thus, thyroid and adrenal function have to be assessed in case

of hyponatremia and eventual substitutive treatment has to be started as soon as possible, with L-Thyroxine (1-4 mcg/kg/daily) and/or Hydrocortison (10 mg/m^2/daily).

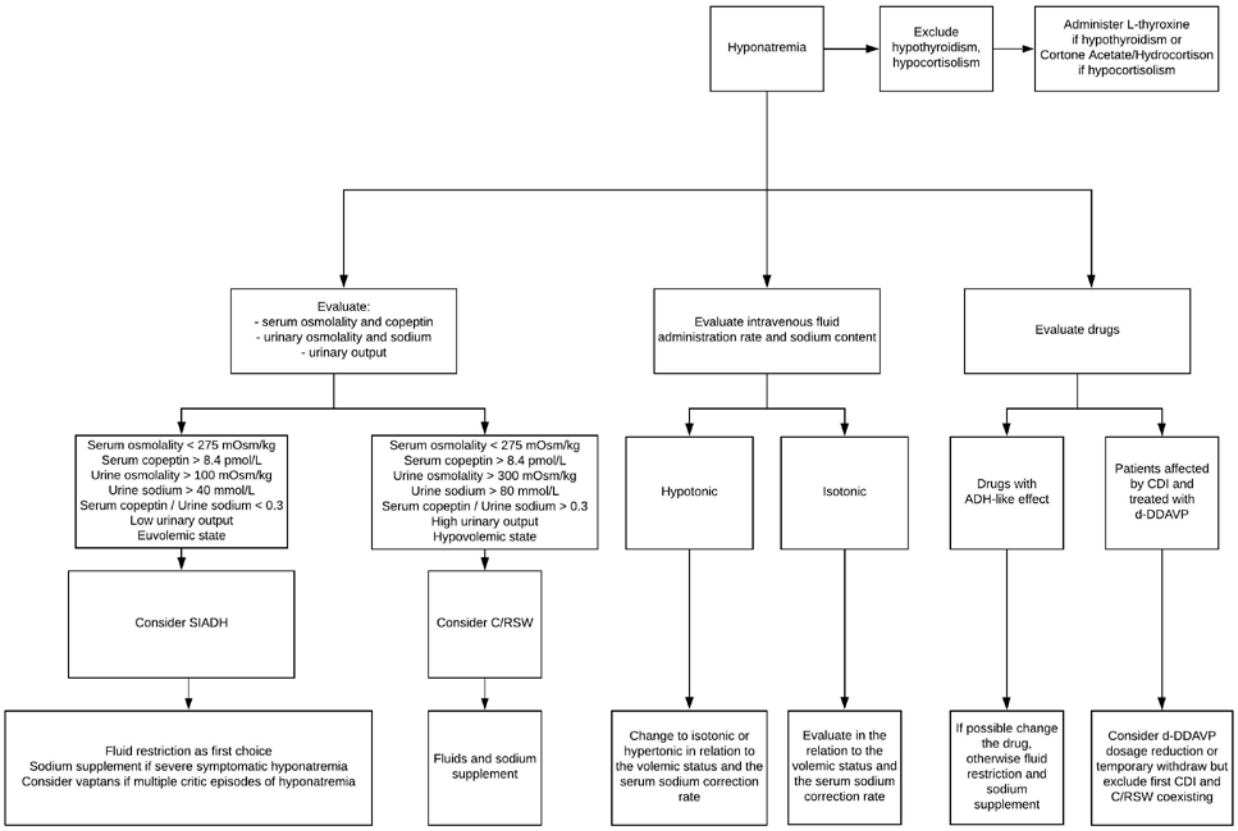

Figure 1. Clinical management of hyponatremia in children with pituitary-suprasellar tumors

Tabella:

Prima box in basso →recurrent episodes of severe hyponatremia

Quarta Box in basso→ evaluate in relation to…

Quinta box in basso→ drug; otherwise fluid restriction and sodium supplementation

Syndrome of inappropriate secretion of ADH (SIADH). The syndrome of inappropriate secretion of ADH (SIADH) is a condition of euvolemic hyponatremia [35]. The typical presentation includes hyponatremia (<135 mmol/l), low serum osmolality (<275 mOsm/kg), inappropriate high urine osmolality (>100 mOsm/kg) and euvolemia with diuresis contraction and lowered osmotic threshold for thirst. No water retention symptoms are usually present, as normally only one third of the body water content is in the extra-cellular compartment. SIADH is mainly a chronic condition, but in oncologic patients it often represents an acute and dramatic event, difficult to manage.

The treatment of chronic hyponatremia due to SIADH requires fluid restriction (20 ml/kg/24 hours or about 500 ml less than daily urinary output), while the treatment of acute and severe symptomatic hyponatremia may need intravenous sodium supplementation through hypertonic solutions [37-45]. Obtaining or maintaining fluid restriction is often a challenge for the poor

compliance of these subjects that have a lower thirst threshold [45]. In our experience, many times fluid restriction is difficult to achieve also for the concomitant use of other therapeutic agents (e.g. antibiotics or chemotherapics needing larger amounts of fluids) or for the high proportion of fluids administrated to preserve kidney function. In these cases orally sodium supplementation (1-2 g/day) could also be necessary.

When the underlying disease responsible for the SIADH is a chronic condition, i.e. a large tumor mass in the suprasellar region, a chronic hyponatremia with potential severe neurological symptoms as seizures and consciousness alteration may occur. This complication is the one that may drive the decision to use a drug-class called vaptans, aquaretic agents able to induce poliuria [46-47]. For that regimen children have to be hospitalized, starting with a low-dose; afterwards, the dosage should be modulated by monitoring serum sodium and urine output for at least 48-72 hours. To avoid rapid fluctuation of serum sodium level, during this regimen patients can have free access to water, but should be strictly monitored for sodium and osmolarity changes, and previous hyponatremia treatments need to be progressively withdrawn. Usually serum sodium normalized in 24-48 hours, while urinary output stabilized in 15-20 days, for the electrolyte-free aquaresis caused by tolvaptans. However, few studies have so far been published on tolvaptan utilization in the pediatric age; for patients under 18 years of age, both in Europe and in the USA, nowadays it is considered an off-label drug. In euvolemic SIADH-related hyponatremia in the pediatric age, even if actual data indicate a good efficacy and safety, further studies are needed to strengthen these preliminary results [46-50].

Cerebral/renal salt wasting syndrome (C/RSW). The cerebaral salt wasting (CSW) syndrome, more correctly defined as cerebral-renal salt wasting syndrome (C/RSW), is a hypovolemic hyponatremic acute condition whose pathogenetic mechanism is still controversial. It seems related to a reduction of renal sympathetic stimulation, in which brain natriuretic peptides are also involved, through the suppression of renin, aldosterone and AVP secretion [13, 19-22, 36]; the final result is renal sodium resorption decrease, with consequent hypovolemic state. In C/RSW, the hypovolemic stimulus is more effective on AVP secretion than the hypo-osmolar one; the AVP release is then responsible of the hyponatremic state despite the low serum osmolality. Typical features of this condition are hyponatremia, hypovolemia and renal sodium loss with consequent increased diuresis 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 euvolemia is typical of the SIADH condition. The main clinical and biochemical features of SIADH and C/RSW are represented in Table 1.

Table 1. Main clinical and biochemical differences between SIADH and C/RSW [13, modified].

	SIADH	C/RSW
Body weight	Increased	Stable or decreased
Arterial blood pressure	Stable or increased	Decreased
Dehydration	No	Yes
Serum sodium	Decreased	Decreased
Urine sodium	Increased	Increased
Urine output	Decreased	Increased
Serum osmolality	Decreased	Decreased
Urine osmolality	Increased	Increased
Urine osmolality/serum osmolality	>1	>1
Serum urea	Decreased	Normal/Increased
Serum uraete	Decreased	Increased
Hematocrite	Decreased	Normal/Increased
Serum ADH	Increased	Firstly decreased and then increased (but lower than in SIADH)
Serum copeptin	Increased	Firstly decreased and then increased (but lower than in SIADH)
Serum natriuretic peptide	Increased	Increased
Serum copeptin/urinary sodium ratio	<0.3	>0.3

The C/RSW treatment requires fluid and salt supplementation in order to sustain circulation and renal sodium loss [13,15]. Daily sodium supplement is showed in Table 2, whereas fluid need is larger, amounting at 80-100 ml/kg/day. When hyponatremia persists fludrocortisone at 0.025-1 mg/day may be used.

Table 2. Daily sodium intake in relation to hyponatremia.

Serum sodium (mmol/l)	Sodium daily administration
130-135	2-3 mmol/kg/day
124-130	5-6 mmol/kg/day
<124	6-10 mmol/kg/day

A rapid serum sodium correction has to be avoided; the gold standard sodium correction over time should be of 4-6 mmol/l in the first 4-6 hours, of 10-12 mmol/l in the first 24 hours, <18 mmol/l in the first 48 hours [13, 50].

Hypotonic fluids and drug-related hyponatremia

To avoid sodium and water homeostasis imbalance and to promptly adapt the d-DDAVP dosage in patients affected by CDI, serum sodium and osmolality, urinary osmolality and urinary output have to be carefully monitored during chemotherapy or radioteraphy. The main risk factors during chemioterapy are the high rate of hypotonic maintenance fluids at which the subject are subjected, the use of potential ADH-like drugs (e.g. vincristine, vinblastin, iphosphamide and cysplatin) and the nausea/vomiting-induced SIADH; during radiotherapy, the neuronal tissue inflammatory state and/or the tumor mass volume modification may lead to C/RSW in exceptional cases [34].

Indeed during chemotherapy large amounts of fluids are required to preserve kidney functionality and to avoid chemotherapics toxicity; however, hypotonic fluids have to be avoided in patients affected by brain tumors in pediatric age, especially when the neuroanatomical circuits of thirst and AVP release are injured. From our personal experience, even supported by literature data, in that situation the gold standard maintenance fluids are represented by isotonic solutions [52, 53].

In patients with CDI and concomitant SIADH, fluid restriction is needed and 1-deamino-8-D-Arginine-Vasopressin (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 an insufficient d-DDAVP dosage from coexisting of the CDI and C/RSW conditions [54-56]. Low urine sodium and low urine osmolality should help in orienting towards a d-DDAVP dose increase; 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 as 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 sodium content of eventually intravenous administered fluids as well as the oral ingested fluid amount and the thirst sensation have to be accurately quantified. Any drug interfering with serum sodium levels have to be considered as well. The further biochemical evaluation should include a serum sample for blood count, potassium, creatinine, urea, osmolality and copeptin and an urine sample for density, osmolality and sodium.

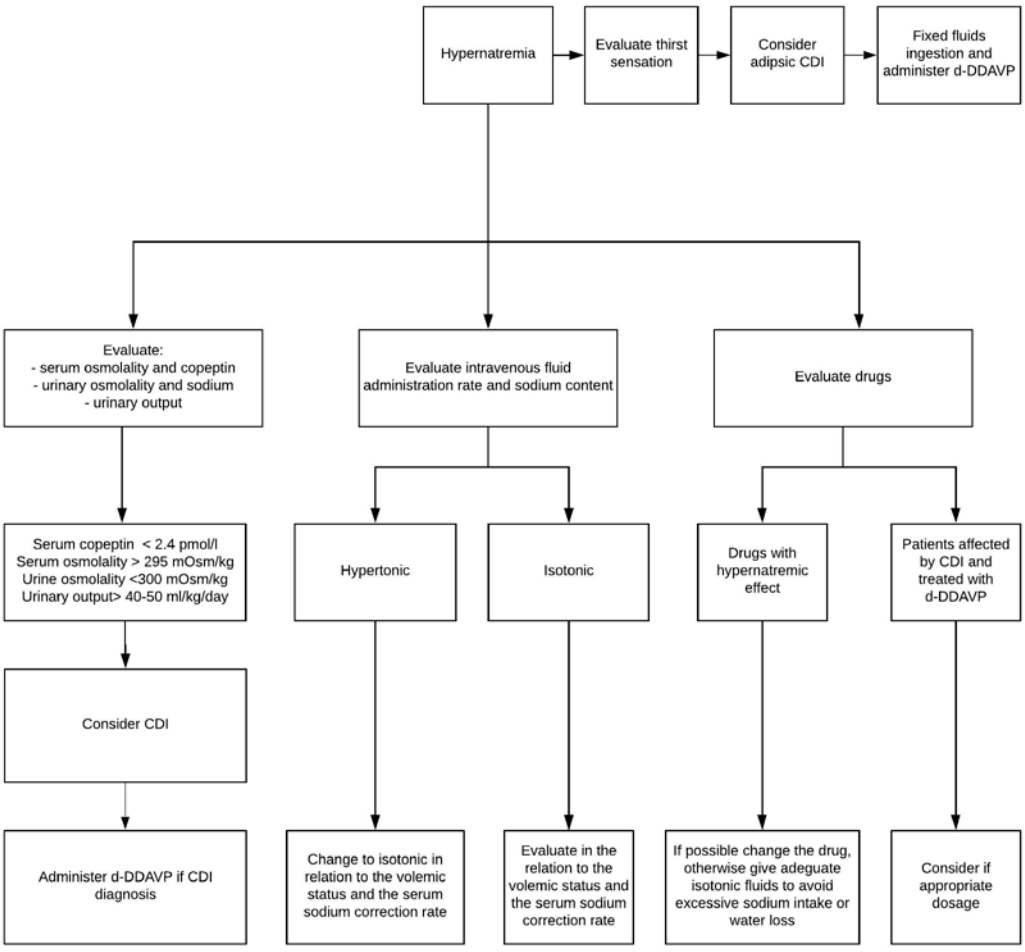

Figure 2. Clinical management of hypernatremia in children with pituitary-suprasellar tumors

Tabella:

Ultima box in alto a dx → fixed fluid ingestion and d-DDAVP administration

Seconda fila, box centrale → evaluate intravenous fluid with sodium rate and content

Terza fila, ultima box a dx → d-DDAVP treatment in patients with CDI

Clinical management of the main hypernatremic conditions

Central Diabetes Insipidus (CDI). 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 [27,33,57,59]. When the compensatory mechanism of polydipsia fails, dehydration, vomiting, fever, irritability, sleep disorders and failure to thrive develop.

Serum sodium, osmolality and copeptin and urine osmolality are required as a first step biochemical evaluation when CDI is suspected [27, 33, 57]. Serum sodium >145 mmol/l, serum osmolality >300 mOsm/kg and urine osmolality <300 mOsm/kg are indicative of the condition. The standard diagnosis of CDI requires water deprivation test and desmopressin (1-deamine-8-D-arginin-vasopressin, DDAVP) test to distinguish CDI from nephrogenic DI or primary polidipsia, but in patients with already diagnosed brain tumors it is not necessary. The most frequent tumoral lesions on the pituitary area causing CDI are germinoma, Langerhans cells histocytosis and pinealoma [13]. Neurosurgical injury of the pituitary stalk and/or of the neurohypophysis is another common cause of acquired CDI, especially when a large tumor in the sellar/suprasellar region is present, as in case of ganglioglyoma or craniopharyngioma. The CDI onset mostly depends by the neuro-surgeon approach (trans-cranial vs trans-sphenoidal) and by the resection wideness (conservative vs destructive). CDI may be permanent in case of AVP-releasing neuronal loss or transient during the neurosurgery or in the next post-operative hours. In 3.4% up to 22.5% of cases a “triphasic” pattern which can be present: transient CDI is present in the first 24-48 hours after the surgery, for the edema and pituitary stalk inflammation; subsequently, a 1-10 days lasting phase is characterized by neurohypophyseal cell necrosis and consequent AVP-stored secretion causing SIADH; the third phase, occurring when more than 90% of neurohypophyseal function is lost, is characterized by a permanent CDI and happens in up to 75-85% of patients undergoing sella/suprasellar neuro-surgery [13, 15, 27-28, 33, 55]. Patients that have experienced the “triphasic” pattern usually develop permanent CDI [28]; thus, neurosurgery is an important step in pituitary/suprasellar tumors treatment and sodium and fluids management during the intra and post-operative phase is quite challenging as both hypernatremia or hyponatremia may occur [61].

In children with pre-existing CDI, d-DDAVP is regularly administered in the 6-12 hours before surgery, whereas in children without pre-existing CDI, copeptin measurement may orientate

towards the probability of developing CDI [60]. To avoid intra-operative water intoxication in patients with CDI, in the morning of surgery the d-DDVAP treatment should be interrupted. Regardless of previous conditions of sodium metabolism imbalance, during neurosurgery fluids infusion rate and concentration are calculated on the basis of hourly registered serum sodium, diuresis and urinary osmolality; when serum sodium is >147 mmol/l and urine osmolality <300 mmol/kg H_2O and urinary output >2.5 ml/kg/h for more than 2 hours, in children < 2yrs or > 2 yrs of age 0.5-1 mcg of d-DDAVP should be intravenously administered, respectively.

In the 24 hours after surgery, serum sodium and osmolality, urinary osmolality and output are measured and recorded every 4 hours; hydro-electrolytic infusion is calculated on the basis of the aforementioned criteria as during the neuro-surgery and intravenous d-DDVAP is administered when necessary, until patients wake-up and experience a sense of thirst.

Furthermore, during the intra-and post-operative period (24-48 hours) continuous intravenous hydrocortisone at stress dosage is administered.

When the clinical conditions allow oral ingestion, the hydro-electrolytic infusion should be progressively reduced, oral intake of fluids progressively increased and eventual hormonal substitutive treatment for hypothyroidism, hypocortisolism and CDI administered again by mouth [14].

To detect and treat late hyponatremia or transient/permanent diabetes insipidus, sodium and water metabolism should be then evaluated up to 7-14 days after surgery [15,16,58].

The treatment of permanent CDI consists of d-DDAVP, which can be orally, sublingually, intranasally or intravenously administrated [27, 33, 57, 59]. Actually, the most used way for oral treatment is the sublingual formulation, with an initial dose of 1-4 mcg/kg/day in 2-3 administrations, starting with the lowest dose for the high renal response to increase it later, on the basis of polyuria-polydipsia signs and serum sodium levels.

Adipsic central diabetes insipidus (aCDI). The adipsic central diabetes insipidus (aCDI) is a particular form of CDI caused by hypothalamic osmoreceptors, supraoptic/paraventricular or neurohypophyseal nuclei injuries. Despite serum osmolality increase, patients lacks thirst sensation, thus becoming 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 DDAVP administration and frequent supply of liquids in relation to body weight (40 ml/kg + 300 ml/mq perspiratio) [13, 15, 27, 33].

Hypertonic fluids and drug-related hypernatremia

To avoid secondary hypernatremia, fluids intravenously administered have to be always assessed for their sodium rate and content; hypertonic solutions should be changed in isotonic fluids in relation to the volemic status and to the sodium correction rate [52]. Drug-related hypernatremia may be present when osmotic diuretics are administered. In children with prior CDI diagnosis, in case of persisting hypernatremia, d-DDAVP dosage has to be corrected.

CONCLUSIONS

Sodium homeostasis disorders are the most frequent electrolyte derangements observed in oncologic pediatric patients. Among these conditions, pituitary-suprasellar tumors are at higher risk of developing such complications for injuries in the neuroanatomical circuits of thirst and AVP release. Sodium homeostasis maintenance is fundamental not only for the neuropsychomotor development, but also for a better response to treatment and for the disease survival rate. Only a close multidisciplinary cooperation between pediatric oncologists and endocrinologists allows the achievement of the best management in such severe and complex disorders.

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

REFERENCES

1. Gizowski C, Bourque CW (2008) The neural basis of homeostatic and anticipatory thirst. Nat Rev Nephrol 14(1):11-25.
2. Zimmerman CA, Leib DE, Knight ZA (2017) Neural circuits underlying thirst and fluid homeostasis. Nat Rev Neurosci 18(8):459-469.
3. Andersson B (1978) Regulation of water intake. Physiol Rev 58:582-603.
4. McKinley MJ, Johnson AK (2004) The physiological regulation of thirst and fluid intake.. News Physiol Sci 19:1-6.
5. Verney EB (1947) The antidiuretic hormone and factors which determine its release. Proc Roy Soc B 135:25-106.
6. McKinley MJ, Cairns MJ, Denton DA, Egan G, Mathai ML, Uschakov A, Wade JD, Weisinger RS, Oldenfield BJ (2004) Physiological and pathophysiological influences of thirst. Physiol Behav 81:795-803.

7. McKinley MJ, Congiu M, Denton DA, Park RG, Penschow J, Simpson JB, Tarjan E, Weisinger RS, Wright RD (1984) The anterior wall of the third cerebral ventricle and homeostatic response to dehydration. J Physiologie (Paris) 79:421-427.
8. Hoorn EJ, Geary D, Robb M, Halperin ML, Bohn D (2004) Acute hyponatremia related to intravenous fluid administration in hospitalized children: an observational study. Pediatrics 113:1279-1284.
9. Ranadive SA, Rosenthal SM (2009) Pediatric disorders of water balance. Endocrinol Metab Clin N Am 38:663-672.
10. Williams CN, Belzer JS, Riva-Cambrin J, Presson AP, Bratton SL (2014) The incidence of postoperative hyponatremia and associated neurological sequelae in children with intracranial neoplasms. J Neurosurg Pediatr 13(3):283-90.
11. Balachandran K, Okines A, Gunapala R, Morganstein D, Popat S (2005) Resolution of severe hyponatraemia is associated with improved survival in patients with cancer. BMC Cancer. 15:163.
12. Williams CN, Riva-Cambrin J, Presson AP, Bratton SL (2015) Hyponatremia and poor cognitive outcome following pediatric brain tumor surgery. J Neurosurg Pediatr 15(5):480-487.
13. Edate S, Albanese A (2015) Management of electrolyte and fluid disorders after brain surgery for pituitary/suprasellar tumours. Horm Res Paediatr 83(5):293-301.
14. Harrington M, Casella S (2012) Pituitary tumors in childhood. Curr Opin Endocrinol Diabetes Obes 19(1):63–67
15. Matarazzo P, Genitori L, Lala R, Andreo M, Grossetti R, de Sanctis C (2004) Endocrine function and water metabolism in children and adolescents with treated intra/parasellar tumours. J Ped Endocrinol Metab 17:1487-1495.
16. Williams CN, Riva-Cambrin J, Bratton SL (2016) Etiology of postoperative hyponatremia following pediatric intracranial tumor surgery. J Neurosurg Pediatr 17(3):303-309.
17. Berardi R, Rinaldi S, Caramanti M, Grohè C, Santoni M, Morgese F, Torniai M, Savini A, Fiordoliva I, Cascinu S (2016) Hyponatremia in cancer patients. Time for a new approach. Crit Rev Onc 102:15-25.
18. Albanese A, Hindmarsh P, Stanhope R (2001) Management of hyponatremia in patients with acute cerebral insults. Arch Dis Child 85:246-251.
19. Hardesty DA, Kilbaugh TJ, Storm PB (2012) Cerebral salt wasting syndrome in post-operative pediatric brain tumor patients. Neurocrit Care 17:382-387.

20. Briceno LG, Grill J, Bourdeaut F, Doz F, Beltrand J, Benabbad I, Brugieres L, Dufour C, Valteau-Couanet D, Guerrini-Rousseau L, Aerts I, Orbach D, Alpetite C, Samara- Boustani D, Pinto G, Simon A, Touraine P, Sainte-Rose C, Zerah M, Puget S, Elie C, Polak M (2014) Water and electrolyte disorders at long term post-treatment follow-up in paediatric patients with suprasellar tumours include unexpected persistent cerebral salt-wasting syndrome. Horm Res 82:364-371.
21. Bettinelli A, Longoni L, Tammato F, Farè PB, Garzoni L, Bianchetti MG (2012) Renal salt-wasting syndrome in children with intracranial disorders. Pediatr Nephrol 27:733-739.
22. Jiménez R, Casado-Flores J, Nieto M, García-Teresa MA (2006) Cerebral salt wasting syndrome in children with acute central nervous system injury. Pediatr Neurol 35(4):261-263.
23. Williams C, Simon TD, Riva-Cambrin J, Bratton SL (2012) Hyponatremia with intracranial malignant tumor resection in children.. J Neurosurg Pediatr 9(5):524-529.
24. Rose S, Horne V, Howell J, Lawson S, Rutter M, Trotman G, Corathers S (2016) Late endocrine effects of childhood cancer. Nat Rev Endocrinol 12: 319-336.
25. Hannon MJ, Finucane FM, Sherlock M, Agha A, Thompson CJ (2012) Clinical review: disorders of water homeostasis in neurosurgical patients. J Clin Endocrinol Metab 97(5):1423–1433
26. Alharfi IM, Stewart TC, Kelly SH, Morrison GC, Fraser DD 2013) Hypernatremia is associated with increased risk of mortality in pediatric severe traumatic brain injury. J Neurotrauma 30(5):361–366
27. Di Iorgi N, Morana G, Napoli F, Allegri AEM, Rossi A, Maghnie M (2015) Management of diabetes insipidus and adipsia in the child. Best Pract Res Clin Endocrinol Metab 29:415-436.
28. R. W. J. Kruis, A. Y. N. Schouten van Meeteren, M. J. J. Finken, W. Oostdijk, A. S. P. van Trotsenburg, A. M. Boot, H. L. Claahsen van der Grinten, E. J. van Lindert, K. S. Han, E. W. Hoving, E. M. C. Michiels, H. M. van Santen. Management and consequences of postoperative fluctuations in plasma sodium concentration after pediatric brain tumor surgery in the sellar region: a national cohort analysis. Pituitary (2018) 21:384–392 https://doi.org/10.1007/s11102-018-0886-2
29. Kristof RA, Rother M, Neuloh G, Klingmüller D (2009) Incidence, clinical manifestations, and course of water and electrolyte metabolism disturbances following transsphenoidal pituitary adenoma surgery: a prospective observational study. J Neurosurg 111(3):555–562

30. Ciric I, Ragin A, Baumgartner C, Pierce D (1997) Complications of transsphenoidal surgery: results of a national survey, review of the literature, and personal experience. Neurosurgery 40(2):225– 236.
31. Pratheesh R, Swallow DMA, Rajaratnam S, Jacob KS, Chacko G, Joseph M et al (2013) Incidence, predictors and early postoperative course of diabetes insipidus in paediatric craniopharygioma: a comparison with adults. Childs Nerv Syst 29(6):941–949
32. Elliott RE, Jane JA Jr, Wisoff JH (2011) Surgical management of craniopharyngiomas in children: meta-analysis and comparison of transcranial and transsphenoidal approaches. Neurosurgery 69(3):630–643
33. Di Iorgi N, Napoli F, Allegri AEM, Maghnie M (2012) Diabetes insipidus–diagnosis and management. Horm Res Paediatr 77:69–84.
34. Liao H, Zhu Z, Rong X, Wang H, Peng Y. Hyponatremia is a potential predictor of progression in radiation induced brain necrosis:a retrospective study. BMC Neurol. 2018 Aug 29;18(1): 30. doi: 10.1186/s12883-018-1135-z.
35. Cuesta M, Thompson CJ(2016) The syndrome of inappropriate antidiuresis (SIAD). Best Pract Res Clin Endocrinol Metab 30: 175-187.
36. Tolunay O, Celik T, Celik Ü, Kömür M, Yağcı-Küpeli B (2015) Cerebral salt wasting in pediatric critical care; not just a neurosurgical disorder anymore. Neuroendocrinol Lett 36(6):578–582.
37. Rivkees RA (2008) Differentiating appropriate antidiuretic hormone secretion, inappropriate antidiuretic hormone secretion and cerebral salt wasting: the common, uncommon, and misnamed. Curr Opin Pediatr 20:448-452.
38. Oh JY, Shin JI (2015) Syndrome of inappropriate antidiuretic hormone secretion and cerebrla/renal salt wasting syndrome: similarities and differences. Front Pediatr 146:1-5.
39. Wright WL (2012) Sodium and Fluid Management in Acute Brain Injury. Curr Neurol Neurosci Rep 12:466–473.
40. Cuesta M, Garrahy A, Thompson CJ (2016) SIAD: practical reccomendations for diagnosis and management. J Endocrinol Invest 39:991-1001.
41. Gross P (2012) Clinical management of SIADH. Ther Adv Endocrinol Metab 3(2):61-73.
42. Grant P, Ayuk J, Bouloux P, Cohen M, Cranston I, Murray R, Rees A, Thatcher N, Grossman A (2015) The diagnosis and management of inpatient hyponatraemia and SIADH.. Eur J Clin Invest 45(8):888–894.

43. Laville M, Burst V, Peri A, Verbalis J (2013) Hyponatremia secondary to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH): therapeutic decision-making in real-life cases. Clin Kidney J 6[Suppl1]:i1–i20.
44. Verbalis JG, Greenberg A, Burst V, Haymann JP, Johannsson G, Peri A, Poch E, Chiodo JA 3rd, Dave J. Diagnosing and Treating the Syndrome of Inappropriate Antidiuretic Hormone Secretion. Am J Med. 2016 May;129(5):537.e9-537.e23. doi:10.1016/j.amjmed.2015.11.005 Epub 2015 Nov 14
45. Winzeler B, Lengsfeld S, Nigro N, Suter-Widmer I, Schutz P, Srici B, Bally M, Blum C, Bock A, Huber A, Muller B, Christ-Crain M (2016) Predictors of nonresponse to fluid restriction in hyponatremia due to the syndrome of inappropriate antidiuresis. J Intern Med 280:609-617.
46. Marx-Berger D, Milford DV, Bandhakavi M, Van't Hoff M, Kleta R, Dattani M, Bockenhauer D (2016) Tolvaptan is successful in treating inappropriate antidiuretic hormone secretion in infants. Acta Paediatr 105(7):334-337.
47. Tuli G, Tessaris D, Einaudi S, De Sanctis L, Matarazzo P (2017) Tolvaptan utilization in children with chronic hyponatremia due to inappropriate antidiuretic hormone secretion (SIADH). Three case reports and review of the literature. J Clin Res Pediatr Endocrinol 9(3):288-292.
48. Higashi K, Murakami T, Ishikawa Y, Itoi T, Ohuchi H, Kodama Y, Honda T, Masutani S, Yamazawa H, Senzaki H, Ishikawa S (2016) Efficacy and safety of tolvaptan for pediatric patients with congestive heart failure. Multicenter survey in the working group of the Japanese Society of PEdiatric Circulation and Hemodynamics (J-SPECH). Int J Cardiol 205:37-42.
49. Regen RB, Gonzalez A, Zawodniak K, Leonard D, Quigley R, Barnes AP, Koch JD (2013) Tolvaptan increases serum sodium in pediatric patients with heart failure. Pediatr Cardiol 34(6):1463-1468.
50. Muto S, Kawano H, Higashihara E, Narita I, Ubara Y, Matsuzaki T, Ouyang J, Torres VE, Horie S (2015) The effect of tolvaptan on autosomal dominant polycystic kidney disease patients: a subgroup analysis of the Japanese patient subset from TEMPO 3:4 trial. Clin Exp Nephrol 19(5):867-877.
51. Aylwin S, Burst V, Peri A, Runkle I, Thatcher N (2015) ‘Dos and don’ts’ in the management of hyponatremia, Current Medical Research and Opinion 9:1755-1761.
52. Moritz ML, Ayus JC. Prevention of hospital-acquired hyponatremia: a case for using isotonic saline. Pediatrics 2003;111:227-30.

53. Choong K, Arora S, Cheng J, Farrokhyar F, Reddy D, Thabane L, et al. Hypotonic versus isotonic maintenance fluids after surgery for children: a randomized controlled trial. Pediatrics 2011;128:857-66.
54. Ferry RJ, Kesavulu V, Kelly A, Levitt Katz LE, Moshang T (2001) Hyponatremia and polyuria in children with central diabetes insipidus: Challenges in diagnosis and management. J Pediatr 138:744-747.
55. Finken MJ, Zwaveling-Soonawala N, Walenkamp MJ, Vulsma T, van Trotsenburg AS, Rotteveel J (2011) Frequent occurrence of the triphasic response (diabetes insipidus/hyponatremia/diabetes insipidus) after surgery for craniopharyngioma in childhood. Horm Res Paediatr 76(1):22-26.
56. Wu X, Zhou X, Gao L, Wu X, Fei L, Mao Y, Hu J, Zhou L (2016) Diagnosis and Management of Combined Central Diabetes Insipidus and Cerebral Salt Wasting Syndrome After Traumatic Brain Injury. World Neurosurg 88:483-487
57. Dabrowski E, Kadakia R , Zimmerman D, Lurie RH (2016) Diabetes insipidus in infants and children. Best Pract Res Clin Endocrinol Metab 30:317-328.
58. Tuli G, Tessaris D, Einaudi S, Matarazzo P, De Sanctis L (2018) Copeptin role in polyuria-polydipsia syndrome differential diagnosis and reference range in paediatric age. Clin Endocrinol (Oxf) 88(6):873-879.
59. Elder CJ, Dimitri PJ (2017) Diabetes insipidus and the use of desmopressin in hospitalised children. Arch Dis Child Educ Pract Ed 102:100–104.
60. Winzeler B, Zweifel C, Nigro N, Arici B, Bally M, Schutz P, Blum CA, Kelly C, Berkmann S, Huber A, Gentili F, Zadeh G, Landolt H, Mariani L, Muller B, Christ-Crain M. (2015) Postoperative copeptin concentration predicts diabetes insipidus after pituitary surgery. J Clin Endocrinol Metab 6:2275-2282.
61. Matarazzo P, Tuli G, Verna F, Tessaris D, Fiore L, Mussa A, Repici M,. Lala R. Management of sodium metabolism derangements in children treated for hypothalamic-hypophyseal tumours. (2010) J. Pediatr Biochem. 1;4:289-296.