Water and Electrolyte Disorders at Long-Term Post-Treatment Follow-Up in Paediatric Patients with Suprasellar Tumours Include Unexpected Persistent Cerebral Salt-Wasting Syndrome

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Key Words

Electrolyte disorders · Hyponatraemia · Suprasellar tumours · Diabetes insipidus · Cerebral salt-wasting syndrome

Abstract

Background: Patients with brain tumours have a high risk of water and electrolyte disorders (WED). Postsurgery diabetes insipidus (DI) may be transient or permanent, the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and cerebral salt-wasting syndrome (CSWS) are usually transient. **Methods:** Retrospective study, including patients with suprasellar tumours, treated at Hôpital Necker, Institut Gustave-Roussy or Institut Curie, in Île-de-France, between 2007 and 2011. WED were noted if they persisted >1 month after surgery. **Results:** 159 patients were included, 54.1% girls,

43.9% boys. Tumour types were: glioma (43.4%), craniopharyngioma (43.4%), germinoma (11.3%), others (1.9%). Age at diagnosis was 7.1 ± 4.6 years. The median time from end of treatment was 1.9 (0–7.8) years. DI was the most frequent disorder after tumour treatment (50.3%) and was significantly associated with surgery ($p < 0.001$). Persistent CSWS was present in 3.6%, persistent SIADH in 1.3%. Two cases of hyponatraemia were due to adipsia. Thyrotropin deficiency after treatment was noted in 68.9% of patients tested, adrenocorticotropin deficiency in 66.2%. **Conclusions:** Patients with suprasellar tumours have a high incidence of long-term WED, mainly DI. Assessment of thyrotroph and corticotroph

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function, and thirst sensation, is necessary to diagnose and manage these disorders correctly. CSWS may be persistent in few patients and requires special attention to prescribe the appropriate care.

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Introduction

Brain tumours are the most frequent solid tumours during childhood and adolescence [1, 2] and also the principal cause of mortality from childhood cancer [2, 3].

Tumours which originate in or near the sella turcica, or those with extensions towards this area, may produce signs of hormonal disorders, including anterior and posterior pituitary deficiencies, prior to diagnosis [2–4] or as a consequence of antitumour treatment [1, 5].

Posterior pituitary disorders, which manifest as water and electrolyte disorders (WED), may be among the potential complications at diagnosis and during treatment. These disorders can be classified as hyponatraemic, diabetes insipidus (DI) being the principal cause, or hyponatraemic, with many different causes [6–8] (table 1) including disturbances related to the tumour, such as hormonal deficiencies (thyrotroph or corticotroph), drug-related hyponatraemia, renal salt and water loss, syndrome of inappropriate antidiuretic hormone (SIADH) and cerebral salt-wasting syndrome (CSWS).

Many studies have focused on sodium disturbances during the acute phase following brain surgery [5, 9–14], but only 2 address hyponatraemia more than 1 month after the initial acute phase [11, 15] and its persistence over time. DI has been traditionally regarded as the main long-term event following brain tumour treatment, whereas SIADH and CSWS are described in the literature as acute phase disorders, which are usually resolved rapidly, in a few days, and rarely last longer than 30 days [12, 15, 16].

Most studies in populations with brain tumours include all tumour types and localizations, so cohorts exclusively constituted of patients with sellar and suprasellar tumours are rare [11, 17]. An exception to this rule are craniopharyngiomas, which are a very well-studied subgroup [10, 18–20].

Concomitant anterior pituitary hormonal disturbances may also play an important role in water regulation disorders. Hypocortisolism may cause hyponatraemia through an increase in ADH levels and also by impairment of free water excretion [21, 22]. Hypothyroidism may also cause hyponatraemia, through impairment of free water excretion caused by a decrease in cardiac out-

put and glomerular filtration rate, as well as increased peripheral vascular resistance [7, 21, 23]. However, this is usually observed in severe forms of hypothyroidism and is much less frequent in central hypothyroidism [7].

Sellar tumours may also have extension towards the hypothalamus, so other features such as thirst disorders or reprogramming of the osmotic threshold for ADH secretion secondary to the osmoreceptor centre damage might be present, especially following surgery [7, 12, 18, 22], and thus complicate diagnosis and management.

WED in brain tumour patients may also prove to be a challenge during therapeutic management, since hyperhydration, which is necessary in some chemotherapy protocols, must be dealt with very carefully when these disorders are present [24].

This study aims to assess the prevalence of medium- to long-term persistent DI, SIADH and CSWS in paediatric patients with sellar and suprasellar tumours at least 1 month after surgery.

Materials and Methods

A retrospective study, through the analysis of data from medical records, was conducted. We included patients diagnosed before the age of 18 years with a tumour localized in the sellar and/or parasellar area, including the hypothalamus, optic chiasma and optic nerves (fig. 1), and treated in 1 or more of 3 different clinical institutions between January 2007 and December 2011 (Hôpital Necker-Enfants Malades, Paris; Institut Gustave-Roussy, Villejuif, and Institut Curie, Paris).

Antitumour treatment included surgery, chemotherapy, radiotherapy and a combination of these, according to national or international protocols [25–28] (table 2). Surgery consisted of complete or partial tumour resection. Patients who only had tumour biopsy were noted separately.

Patients who were evaluated in these institutions for a second opinion were excluded, because of the incomplete information available. Patients who received no antitumour treatment (7 patients) or those who died before completion of treatment (2 patients) were also excluded (fig. 1).

Clinical data included age at diagnosis, tumour type, localization and treatment received.

Laboratory values were collected at diagnosis and throughout follow-up, with special attention given to blood electrolytes, urea, creatinine, serum proteins, albumin, urinary electrolytes and osmolality. The presence and time frame of WED, as well as concomitant pituitary hormonal disorders were noted.

Growth hormone deficiency was defined as a growth hormone peak of less than 20 mUI/l after a stimulation test (glucagon test, insulin tolerance test or arginine test). Thyrotroph (thyrotropin) deficiency was defined by low free thyroxine levels with inappropriately low, normal or slightly elevated thyrotropin levels. Corticotroph (adrenocorticotropin) deficiency was diagnosed when there was a low cortisol level at 8.00 h ($<6 \mu\text{g/dl}$); when cortisol was

Table 1. Disorders characterized by hypernatraemia or hyponatraemia

Hypernatraemia	Hyponatraemia
Central DI Nephrogenic DI Adipsic hypernatraemia Physical obstacles to drinking Excessive free water loss (other than DI) Excessive sodium intake	Inappropriate AVP secretion (syndrome of inappropriate hormone, SIADH) <ul style="list-style-type: none">– Nephrogenic SIADH– Tumours– Drugs– CNS disorders– Non-malignant pulmonary disorders– Postoperative hyponatraemia– Adrenal insufficiency– Hypothyroidism Appropriately increased secretion of vasopressin <ul style="list-style-type: none">– Hypovolaemic hyponatraemia from salt and water depletion– Salt and water depletion– Primary sodium deficiency– Hypervolaemic hyponatraemia Water intoxication Cerebral salt wasting

ESPE classification of paediatric endocrine diagnoses, from Wit et al. [8]. AVP = Arginine vasopressin; CNS = central nervous system.

Fig. 1. Population with suprasellar tumours analysed. NF1 = Neurofibromatosis type 1.

normal but $<14\text{--}15\text{ }\mu\text{g/dl}$, a 250- μg tetracosactide (Synacthen[®]) test was performed; an adrenocorticotropin deficiency was noted if the cortisol peak was $\leq 18\text{ }\mu\text{g/dl}$ [29]. The cortisol level at 8.00 h was evaluated at a median time of 0.3 months after surgery (0–35 months). When a Synacthen test was performed, the time elapsed since the last surgery was in all cases more than 3 months.

Precocious puberty was defined by breast development before the age of 8 in girls or increase in testicular volume ($\geq 4\text{ ml}$) before

the age of 9 in boys, biochemical confirmation included luteinizing hormone (LH) and follicle-stimulating hormone (FSH) dosage, with an LH peak $\geq 5\text{ UI/l}$ after a gonadotropin-releasing hormone test, and a peak LH/FSH ratio >0.5 .

Presumed hypogonadism was defined by low levels of oestradiol or testosterone in girls after the age of 13 or boys after the age of 14, according to age and pubertal stage, or the need for sex hormone replacement. Hypogonadism was classified as hypergonad-

Table 2. Study population

	Craniopharyngioma	Germinoma	Glioma	Other	Total
Number of patients	69	18	69	3	159
Percent of total population	43.4	11.3	43.4	1.9	100
Boys/girls	32/37	8/10	32/37	2/1	74/85 (53.5% girls)
Age at diagnosis, years	8.1 (2–15)	12.3 (3.7–18.8)	5.0 (0.4–17.7)	3.2 (0.3–7.7)	7.1±4.6
Surgery	68 (98.6%)	3 (16.7%)	39 (56.5%)	2 (66.7%)	112 (70.4%)
Radiotherapy	65 (94.2%)	18 (100%)	11 (15.9%)	1 (33.3%)	95 (59.8%)
Chemotherapy	0 (0%)	18 (100%)	63 (91.3%)	2 (66.7%)	84 (52.8%)
Others	1 patient (bleomycin injection)	–	–	–	1 (0.6%)
Median follow-up, years	4.0 (1.5–13.8)	3.3 (0.5–7.5)	4.4 (1.1–12.6)	3.3 (1.8–13.8)	4.0 (0.5–13.8)

otrophic when basal LH or FSH levels were superior to the laboratory reference range, or hypogonadotropic, when basal LH and FSH levels were prepubertal or failed to rise in response to a gonadotropin-releasing hormone test.

Endocrine evaluation was performed in the different institutions, and information concerning hormonal dosage (e.g. growth hormone stimulation tests) and treatment was obtained from the medical records.

WED were considered as persistent if still present more than 1 month after surgery or radiotherapy. Those that only appeared during the acute treatment period, and which were resolved in less than 1 month after surgery, were excluded from our analyses.

Patients with hyponatraemia were assessed for concomitant medication which could have had an influence on electrolyte imbalance, such as anti-epileptics and diuretics [30–32]. Hypothyroidism and hypocortisolism were also investigated in all patients with hyponatraemia, and supplements (L-thyroxine or hydrocortisone) were given if necessary. The diagnosis of SIADH was always made after appropriate replacement treatment.

Diagnostic Criteria of WED

DI was diagnosed in patients who had hypernatraemia (>145 mEq/l), polyuria (>3 ml/kg/h), polydipsia as well as an adequate response to treatment with desmopressin (adapted from Hannon et al. [4] and Spasovski et al. [7]).

SIADH was defined by hyponatraemia (<135 mEq/l), inappropriate urine concentration (urinary osmolality >100 mosm/kg), normal or low urine volume and signs of euvoalaemia or hypervolaemia (signs of dilution such as low or lower limit blood proteins or urea nitrogen) and normal or slightly elevated natriuresis (>20 mEq/l) (adapted from Hannon et al. [4] and Spasovski et al. [7]).

CSWS was diagnosed in patients with hyponatraemia, polyuria with signs of dehydration and hypovolaemia (high blood proteins or urea nitrogen), and elevated natriuresis (>40 mEq/l) [4, 9, 21, 33]. There was little data concerning central venous pressure and diuresis, therefore surrogate markers (blood proteins, urea nitrogen) served to assess voalaemia. Exclusion criteria for SWS comprised increased natriuresis in the context of renal tubular dysfunction (elevated serum creatinine or with serum electrolyte disturbances, e.g. hypophosphataemia, hypokalaemia) or after diuretic drug treatment.

Differentiation of CSWS and SIADH was difficult in some cases, since there were patients who presented with euvoalaemic hypona-

traemia suggestive of SIADH, but also with polyuria and an important urinary sodium excretion, which was more compatible with CSWS. Therefore both diagnoses could, and did, coexist, with initial combined therapies which included both water restriction and salt supplementation until the diagnosis was more accurately defined.

Statistics

Statistical analyses were performed using R statistical software. The patient data shown is expressed in mean values ± SD or medians with ranges in parentheses. McNemar's χ^2 test was used to compare qualitative data before and after treatment. The χ^2 test was used to compare qualitative data between independent groups. A p value of less than 0.05 was considered significant.

Results

Cohort Description

A total of 191 patients with suprasellar tumours was initially assessed. Seven patients were excluded since they did not receive antitumour treatment (patients with regular surveillance of a stable glioma in the context of type 1 neurofibromatosis – NF1), 2 patients died before treatment completion, and 23 patients were excluded because of insufficient data. Patients with NF1 who received antitumour treatment were included.

The final cohort included 159 patients (fig. 1). Slightly more than half of them (54.1%) were girls. Age at diagnosis was 7.1 ± 4.6 years.

The tumour types were craniopharyngiomas, germinomas, gliomas (low grade gliomas such as pilocytic astrocytomas) and 3 others (1 case each of enchondroma, chordoma and retinoblastoma; fig. 1; table 2).

The treatment used according to tumour type is summarized in table 2.

Surgical treatment was used in 68/69 patients with craniopharyngioma (98.6%), 39/69 patients with glioma (56.5%), 3/18 patients with germinoma (16.7%) and 2/3 pa-

Table 3. Prevalence of WED at diagnosis and after treatment

		Craniopharyngioma (n = 69)	Germinoma (n = 18)	Glioma (n = 69)	Other (n = 3)	Total
DI	Pretreatment	11/69 (15.9%)	13/18 (72.2%)	1/69 (1.5%)	–	25/159 (15.7%)
	Post-treatment	55/69 (79.7%)	14/18 (77.8%)	10/69 (14.5%)	1/3 (33.3%)	80/159 (50.3%)
SIADH	Pretreatment	–	–	1/69 (1.5%)	–	1/159 (0.6%)
	Post-treatment	–	–	2/69 (2.9%)	–	2/159 (1.3%)
CSWS	Pretreatment	–	–	–	–	0/159 (0%)
	Post-treatment	2/69 (2.9%)	1/18 (5.6%)	3/69 (4.4%)	–	6/159 (3.8%)

tients with other tumour types (66.7%). Sixteen patients had only tumour biopsy, with no further surgical treatment.

External radiotherapy was delivered to 65/69 patients with craniopharyngioma (94.2%), 11/69 patients with glioma (15.9%), 18/18 patients with germinoma (100%) and 1/3 patients with other tumour types (33.3%). In these patients, the dose delivered to the pituitary gland was on average 49.5 ± 8.9 Gy.

Chemotherapy was used in 0/69 patients with craniopharyngioma (0%), 63/69 patients with glioma (91.3%), 18/18 patients with germinoma (100%) and 2/3 patients with other tumour types (66.7%). This type of treatment was mainly based on alkylating agents, platinum compounds and alkaloids in all but 1 of the 84 patients who received it. Patients who received platinum derivatives were at risk of developing secondary tubulopathy and salt loss, which was taken into account when assessing WED. One patient with craniopharyngioma was treated only by an intracystic injection of bleomycin.

At the moment of data analysis, all patients were at least 1 month past surgery or radiotherapy; 16 were still receiving chemotherapy.

At diagnosis of the tumour, DI was already present in 15.7% of the patients (table 3; fig. 2), none of whom recovered from DI during follow-up. SIADH was present at diagnosis in 1 patient with a glioma; this case of SIADH resolved during tumour treatment.

WED after Surgery or Radiotherapy

DI was the most common disorder observed after treatment, appearing in 80/159 patients (50.3%), 55 of which were new cases, not present at diagnosis (table 3). Post-treatment DI was significantly associated with surgical treatment since 53/55 new cases of persistent post-treatment DI had been treated by surgery ($p < 0.001$), and the other 2/55 developed DI within 8 days of biopsy of the

Fig. 2. Proportion of WED before and after treatment, according to tumour type.

tumour, before chemotherapy or radiotherapy started. DI was diagnosed in most cases in the days that followed surgery, with a median time of 2 days (range: 0–476). Of note, in 7 patients, DI was diagnosed between 4 and 15 months after surgery.

Two patients with postsurgical permanent DI (1 patient with a glioma, and 1 with a craniopharyngioma) showed spontaneous recovery after more than 1 year.

SIADH persisting more than 1 month after treatment was rare, occurring in only 2 patients (1.3%); and resolving before 1 year. These 2 patients had a diagnosis of glioma, not NF1 related, and were initially diagnosed as having both CSWS and SIADH at the same time, though only the diagnosis of CSWS was maintained throughout their follow-up.

Fig. 3. Hormonal deficiencies at diagnosis and at the last follow-up visit. GHD = Growth hormone deficiency; TSHD = thyrotropin deficiency; ACTHD = adrenocorticotropin deficiency.

CSWS was present after treatment in 6 patients (3.6%), including the 2 mentioned above with SIADH and CSWS. One of the patients with isolated CSWS had also DI. Only 1 of the patients with CSWS had an elevated intracranial pressure which might have played a part in persistence of his CSWS. The other patients were stable, and no bleeding, infection or tumour progression was documented. For one of the patients, electrolytic balance was restored 1 month after CSWS diagnosis and for another 1 year after. At the moment of data analysis, 4 of the patients were still in need of salt supplements, after 33–43 months. Three out of these 4 patients had an additional thyrotroph deficiency, and 2 had corticotroph deficiency; all received appropriate hormonal substitution treatment. One of the patients received carbamazepine, which might have contributed to the development of hyponatraemia; however, this treatment has been associated with SIADH and not CSWS [30, 32]. The 4 patients who remained with persistent CSWS had at their last medical visit a normal natraemia, receiving 4–6 mEq/kg/day of NaCl. An at-

tempt to lower the salt dose in 2 of the 4 patients after 2 years resulted in hyponatraemia (126 and 132 mEq/l), which was corrected after increase in salt supplementation. The possibility of associated chronic SIADH due to hypothalamic osmoreceptor dysregulation cannot be completely ruled out.

Two cases of hypernatraemia were attributed to adipisia, both in young girls (2 years 2 months and 3 years 9 months) with a diagnosis of hypothalamic glioma. This disorder appeared during the 2 weeks that followed surgery and was corrected after controlled daily water intake had been prescribed. One of the girls had an associated DI.

A total of 3 patients with hyponatraemia were unclassifiable due to insufficient data to establish a diagnosis.

Associated Endocrine Deficiencies

Anterior pituitary deficiencies are shown in figure 3. Thyrotropin deficiency after treatment was noted in 68.9% of patients tested, adrenocorticotropin deficiency in 66.2%. Precocious puberty was reported in 4 patients at

diagnosis, 3 of whom were diagnosed with a glioma (only 1 of them had an associated diagnosis of NF1). Presumed hypogonadism after treatment concerned 35/59 patients who were at an age at which they should have started puberty (>13 years for girls, >14 years for boys). No correlation was found between hormonal deficiencies and WED.

Discussion

This retrospective study focuses on a population of paediatric patients with tumours in the sellar and suprasellar area, and thus constituting a large homogeneous population in terms of tumour localization. Slightly under half of them are in the well-studied craniopharyngioma population.

As expected, the incidence of pretreatment DI (16.3%) was higher in our population than in the brain tumour population overall (around 10.5%) [1], this being linked to the tumour localization. The incidence of DI was particularly high at diagnosis in germinomas (72.2%), which is described in the literature as a feature of this tumour type, mainly because of the frequent involvement of the hypothalamus and pituitary stalk [2, 7, 34, 35]. The post-treatment DI incidence was also higher in our cohort (50.3%) than in brain tumour survivors overall (around 13%) [5]. Postsurgery DI was high in craniopharyngiomas (79.7%) and germinomas (77.8%), comparable to what has been described in the literature (76–96%) [10, 17–20], and slightly higher than expected in gliomas (14.5%).

The challenge of an accurate distinction between SIADH and CSWS has been addressed in several studies [4, 21, 33]. Indeed, differentiation between CSWS and SIADH in our patients was difficult at early stages, since several of these patients had polyuria and elevated natriuresis but with signs of plasma dilution. Some of the patients were treated initially with both fluid restriction and salt supplementation until a more precise diagnosis was possible. However, we noticed that SIADH resolved more rapidly, in under 6 months in all but 1 patient, whereas CSWS seemed to persist longer (4/6 patients with persistent CSWS were still receiving salt supplementation 35–43 months after diagnosis of CSWS). Moreover, 1 patient who attempted to lower salt supplementation 29 months after diagnosis of CSWS developed subsequent asymptomatic hyponatraemia (126 and 129 mEq/l) with elevated natriuresis (298 mEq/l), which indicated a need for continued salt supplementation.

One of the limitations of our study is the lack of complete data for the accurate aetiological diagnosis of hyponatraemia. No patient was reported as having their central venous pressure measured at the occurrence of hyponatraemia, probably because of the stable clinical conditions of most patients, with avoidance of invasive procedures. However, surrogate markers of plasma dilution or concentration were available and were sufficient in most cases to establish a diagnosis.

In this study, pretreatment thyroid function screening was absent in 83% of the patients, and basal cortisol level screening in 88%, both of which may contribute to WED. Even after treatment completion, 16.3% of the patients lacked an endocrine evaluation. Our opinion is that every child diagnosed with a suprasellar tumour should benefit from a minimum basal hormonal screening, including plasma electrolytes and osmolality, even if no clinical signs are present. A subsequent follow-up by a paediatric endocrinologist is necessary in all cases.

We would suggest basal plasma electrolytes, urea, glucose and protein screening be performed at least once before treatment initiation, in order to assess electrolyte balance. Reassessment during follow-up would also be compulsory, especially during surgery and chemotherapy [4, 9–15, 17, 19, 24], after the end of treatment, or if WED is suspected (polyuria, polydipsia, or the development of signs or symptoms suggesting hypo- or hypernatraemia).

In conclusion, our observations suggest it is necessary to keep an eye on electrolyte status in all children with sellar and suprasellar tumours, not only during the acute surgical phase, but also during the follow-up, since, although rare, WED may occur after the end of antitumour treatment. This evaluation should include the hormonal status of the anterior pituitary (especially thyrotroph and corticotroph function), and assessment of thirst sensation.

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Disclosure Statement

The authors declare that there is no conflict of interest.

References

- Shalitin S, Gal M, Goshen Y, Cohen I, Yaniv I, Phillip M: Endocrine outcome in long-term survivors of childhood brain tumors. *Horm Res* 2011;76:113–122.
- Kalifa C, Grill J, Habrand JL, Zerah M, Couanet D, Lellouch-Tubiana A: Tumeurs du système nerveux central; in *Médecine-Sciences* (ed): *Cancers de l'enfant*. Paris, Flammarion, 2008, pp 264–290.
- Pollack IF, Jakacki RI: Childhood brain tumors: epidemiology, current management and future directions. *Nat Rev Neurol* 2011;7:495–506.
- Hannon MJ, Finucane FM, Sherlock M, Agha A, Thompson CJ: Disorders of water homeostasis in neurosurgical patients. *J Clin Endocrinol Metab* 2012;97:1423–1433.
- Vinchon M, Baroncini M, Leblond P, Delestret I: Morbidity and tumor-related mortality among adult survivors of pediatric brain tumors: a review. *Childs Nerv Syst* 2011;27:697–704.
- Czernichow P, Polak M: Testing water regulation; in Ranke MB, Mullis PE (eds): *Diagnostics of endocrine function in children and adolescents*. Basel, Karger, 2011, pp 194–209.
- Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn EJ, Ichai C, Joannidis M, Soupart A, Zietse R, Haller M, van der Veer S, Van Biesen W, Nagler E: Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Eur J Endocrinol* 2014;170:G1–G47.
- Wit JM, Ranke MB, Kelnar CJH: ESPE classification of paediatric endocrine diagnoses. *Horm Res* 2007;68(suppl 2):96–100.
- Hardesty DA, Kilbaugh TJ, Storm PB: Cerebral salt wasting syndrome in post-operative pediatric brain tumor patients. *Neurocrit Care* 2011;17:382–387.
- Finken MJ, Zwaveling-Soonawala N, Walenkamp MJE, Vulsma T, van Trotsenburg ASP, Roozeveel J: Frequent occurrence of the triphasic response (diabetes insipidus/hyponatremia/diabetes insipidus) after surgery for craniopharyngioma in childhood. *Horm Res* 2011;76:22–26.
- Kristof RA, Rother M, Neuloh G, Klingmüller D: Incidence, clinical manifestations, and course of water and electrolyte metabolism disturbances following transsphenoidal pituitary adenoma surgery: a prospective observational study. *J Neurosurg* 2009;111:555–562.
- Segura Matute S, Balaguer Gargallo M, Cambra Lasaosa FJ, Zambudio Sert S, Martín Rodrigo JM, Palomeque Rico A: Fluid and electrolyte disorders following surgery for brain tumors. *An Pediatr (Barc)* 2007;67:225–230.
- Cardoso APD, Dragosavac D, Araújo S, Falcao ALE, Terzi RGG, de Castro M, Marcondes FG, Melo TG, Oliveira RARA, Cintra EA: Syndromes related to sodium and arginine vasopressin alterations in post-operative neurosurgery. *Arq Neuropsiquiatr* 2007;65(3-B):745–751.
- Abla AA, Wait SD, Forbes JA, Pati S, Johnsonbaugh RE, Kerrigan JF, Ng YT: Syndrome of alternating hyponatremia and hyponatremia after hypothalamic hamartoma surgery. *Neurosurg Focus* 2011;30:1–7.
- Blumberg DI, Sklar CA, Wisoff J, David R: Abnormalities of water metabolism in children and adolescents following craniotomy for a brain tumor. *Childs Nerv Syst* 1994;10:505–508.
- Cerdá-Estevé M, Cuadrado-Godia E, Chillaron JJ, Pont-Sunyer C, Cucurella G, Fernández M, Goday A, Cano-Pérez JF, Rodríguez-Campello A, Roquer J: Cerebral salt wasting syndrome: review. *Eur J Intern Med* 2008;19:249–254.
- Matarazzo P, Genitori L, Lala R, Andreo M, Grossetti R, de Sanctis C: Endocrine function and water metabolism in children and adolescents with surgically treated intra/parasellar tumors. *J Pediatr Endocrinol Metab* 2004;17:1487–1495.
- Smith D, Finucane F, Phillips J, Baylis PH, Finucane J, Tormay W, Thompson CJ: Abnormal regulation of thirst and vasopressin secretion following surgery for craniopharyngioma. *Clin Endocrinol (Oxf)* 2004;61:273–279.
- Müller HL: Consequences of craniopharyngioma surgery in children. *J Clin Endocrinol Metab* 2011;96:1981–1991.
- Elowe-Gruau E, Beltrand J, Brauner R, Busiah K, Laborde K, Boddaert N, Zerah M, Alapetite C, Grill J, Touraine P, Sainte-Rose C, Polak M, Puget S: Childhood craniopharyngioma: hypothalamus-sparing surgery decreases the risk of obesity. *J Clin Endocrinol Metab* 2013;98:2376–2382.
- Reynolds RM, Seckl JR: Hyponatremia for the clinical endocrinologist. *Clin Endocrinol (Oxf)* 2005;63:366–374.
- Verbalis J: Disorders of body water homeostasis. *Best Pract Res Clin Endocrinol Metab* 2003;17:471–503.
- Hanna FW, Scanlon MF: Hyponatraemia, hypothyroidism, and role of arginine-vasopressin. *Lancet* 1997;350:755–756.
- Afzal S, Wherret D, Bartels U, Tabori U, Huang A, Stephens D, Bouffet E: Challenges in management of patients with intracranial germ cell tumor and diabetes insipidus treated with cisplatin and/or ifosfamide based chemotherapy. *J Neurooncol* 2010;97:393–399.
- Packer RJ, Lange B, Ater J, Nicholson HS, Allen J, Walker R, Prados M, Jakacki R, Reaman G, Needles MN, Phillips PC, Ryan J, Boyett JM, Geyer R, Finlay J: Carboplatine and vincristine for recurrent and newly diagnosed low-grade gliomas of childhood. *J Clin Oncol* 1993;11:850–856.
- Bouffet E, Jakacki R, Goldman S, Hargrave D, Hawkins C, Shroff M, Hukin J, Bartels U, Foreman N, Kellie S, Hilden J, Etzl M, Wilson B, Stephens D, Tabori U, Baruchel S: Phase II study of weekly vinblastine in recurrent or refractory pediatric low-grade glioma. *J Clin Oncol* 2012;30:1358–1363.
- Laithier V, Grill J, Le Deley MC, Ruchoux MM, Couanet D, Doz F, Pichon F, Rubie H, Frappaz D, Vannier JP, Babin-Boilletot A, Sariban E, Chastagner P, Zerah M, Raquin MA, Hartmann O, Kalifa C: Progression-free survival in children with optic pathway tumors: dependence on age, and the quality of the response to chemotherapy – results of the first French prospective study for the French Society of Pediatric Oncology. *J Clin Oncol* 2003;21:4572–4578.
- Alapetite C, Brisse H, Patte C, Raquin MA, Gaboriaud G, Carrie C, Habrand JL, Thiesse P, Cuillière JC, Bernier V, Ben-Hassel M, Frappaz D, Baranzelli MC, Bouffet E: Pattern of relapse and outcome of non-metastatic germinoma patients treated with chemotherapy and limited field radiation: the SFOP experience. *Neurol Oncol* 2010;12:1318–1325.
- Forest MG: Adrenal function tests; in Ranke MB (ed): *Diagnostics of Endocrine Function in Children and Adolescents*. Basel, Karger, 2003, pp 372–426.
- De Bragança AC, Moyses ZP, Magaldi AJ: Carbamazepine can induce kidney water absorption by increasing aquaporin 2 expression. *Nephrol Dial Transplant* 2010;25:3840–3845.
- Smith D, Moore K, Tormey W, Baylis PH, Thompson CJ: Downward resetting of the osmotic threshold for thirst in patients with SIADH. *Am J Physiol Endocrinol Metab* 2004;287:E1019–E1023.
- Krisiak R, Okopien B: Carbamazepine-induced hyponatremia. *Pol Arch Med Wewn* 2007;117:73–75.
- Harrigan MR: Cerebral salt wasting syndrome. *Crit Care Clin* 2001;17:125–138.
- Sethi RV, Marino R, Niemierko A, Tarbell NJ, Yock TI, MacDonald SM: Delayed diagnosis in children with intracranial germ cell tumors. *J Pediatr* 2013;163:1448–1453.
- Srivatsa A, Majzoub JA: Disorders of water homeostasis; in Lifshitz F (ed): *Pediatric Endocrinology*. New York, Informa Healthcare, 2007, pp 651–692.