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DISORDERS OF WATER AND SODIUM METABOLISM IN CHILDREN

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Water and sodium metabolism is coordinated by an extremely complex regulatory mechanism, which maintains plasma osmolality in a narrow range. Deviations from plasma osmolality led to an action from osmoregulatory system, represented by two principal organs: hypothalamus/posterior pituitary and kidney, organs also influenced by other regulatory systems, as adrenal gland. Disorders of water and sodium metabolism should include a careful clinical assessment associated to laboratory evaluation of antidiuretic hormone and its sensitivity at renal level, renal (including natriuresis, urine culture and renal ultrasound) and adrenal evaluation (hormonal adrenal sampling in each case before any treatment).

Keywords: water, sodium, metabolism, genetics.

INTRODUCTION

Water and sodium metabolism is coordinated by an extremely complex regulatory mechanism, which maintains plasma osmolality in a narrow range for the optimal functioning of the body.

Plasma osmolality is a measure of osmotic substances in plasma, mainly determined by sodium (and the corresponding anions – chloride and bicarbonate), glucose and urea. Thus, plasma osmolality is often calculated using the formula: 2*Na(+)+glucose (mg/dL)/18+BUN (mg/dL)/ 2.8 (BUN-Blood Urea Nitrogen) and the reference range for plasma osmolality is 285–295 mOsm/kg H_2O in adulthood and 275–290 mOsm/kg H_2O in children[1].

Deviations from plasma osmolality led to reaction from the osmoregulatory system, represented by two principal organs: hypothalamus/ posterior pituitary and kidney, organs also influenced by other regulatory systems. This osmoregulatory system is complex, reacting to changes in plasma osmolality, regardless of large variations of water intake/loss[2–4].

HYPOTHALAMUS/POSTERIOR PITUITARY REGION

The hypothalamic-pituitary region is an important component of the osmoregulatory system through the secretion of antidiuretic hormone or arginine vasopressin (AVP). AVP secretion is stimulated by sensors for plasma osmolality (localized in supraoptic and paraventricular hypothalamic region). Human osmotic threshold for AVP secretion is 280 mOsm/kg H_2O[2–6].

Another stimulus of AVP secretion is represented by thirst.

A third stimulus for AVP secretion is represented by sensors for plasma volume, located at the carotid sinus and aortic arch, reaching supraoptic and paraventricular nuclei of hypothalamus through cranial nerves (IX, X). However, these volume sensors are less sensitive than osmolality sensors, only 5–10% change in blood volume will stimulate AVP secretion[2,3]. In addition to these regulators of the hypothalamic-pituitary region (volume, pressure and thirst stimuli), a morpho-functional integrity of the hypothalamic-pituitary region of the organs that

synthesizes (paraventricular, supraoptic), stores and secretes AVP (posterior pituitary) is mandatory[2–4].

Other factors that stimulate the AVP secretion are nausea, hypoglycemia, angiotensin, glucocorticoids[2–5].

KIDNEY

The second main regulator of plasma osmolality is the kidney, by renal collecting duct sensitive to AVP (via the V2R receptor)[2,3]. Thus, aquaporin system 2 stimulation will lead to variations of urinary flow to maintain an optimal water balance.

The kidney also secretes renin, another hormone with an important role in water and sodium homeostasis. Renin is secreted from the juxtaglomerular apparatus under the action of regulatory factors: changes in renal perfusion in the afferent arterioles (renal hypoperfusion), changes in natremia in the distal convoluted tubules at the level of the dense macula (hyponatremia), the sympathetic system through beta-1 adrenergic receptors, hypokalemia. Angiotensin 1, atrial natriuretic peptide, hyperpotassemia decreased the renin secretion by negative feedback[2–4].

Renin stimulates adrenal secretion of aldosterone. Aldosterone, by acting on mineralocorticoid receptors (distal and collecting tubes), has a renal effect on sodium reabsorption and secretion of potassium and H^+ at the renal level. Through this sodium reabsorption effect, aldosterone led to an increase in blood volume and blood pressure. A hypersecretion of aldosterone is responsible of hypernatremia, hypokalemia and metabolic alkalosis. A hyposecretion of aldosterone led to salt loss (hyponatremia), hyperkalemia and metabolic acidosis.

99% of filtered sodium is reabsorbed at the nephron, thus the excreted sodium is equal to ingested sodium[2,3]. Adrenal secretion of aldosterone is mainly stimulated by the renin-angiotensin-aldosterone system, hyperkalemia and ACTH. Mineralocorticoid receptors are influenced by the glucocorticoids.

INITIAL ASSESSMENT OF PATIENTS WITH SODIUM AND WATER HOMEOSTASIS DISORDERS

Clinically, it is important to evaluate – thirst, urinary volume, plasma volume (clinical evaluation by measuring body weight, signs of dehydration or edema). Polyuria is defined as urinary volume over 5 ml/kg/h in infants and over 1500 ml/m^2/24h (50 ml/kg/day) in children[2,3]. In each case, it should be excluded: osmotic diuresis (glucose, urea); intrinsic kidney disease or hypercalcemia.

It is also important to evaluate AVP secretion and sensitivity of the kidney to AVP by determining: copeptin, plasma osmolality, urinary osmolality, plasma and urinary sodium, plasma and urinary potassium, bicarbonates, PH, glycemia, proteinemia, urea, blood urea nitrogen (BUN), creatinine[2–4]. AVP/Copeptin varies with osmotic stimulus and are evaluated compared to plasma osmolality. The adrenal is assessed by determining plasma renin and immunoreactive renin activity, plasma aldosterone, cortisol, ACTH, delta 4 androstenedione, 17 hydroxy-progesterone, urinary steroid profile[2–4]. An important recommendation is to assess urine exam, urine culture and renal ultrasound.

Dehydration test, another useful tool to assess water balance is usually performed between 6pm and 8 am (14h), but in very young children or patients with massive polyuria (volume over 4 liters/24h) the assessment should be performed on shortest period, usually between 8 am and 12 am (4 hours)[2–4]. Every 2 hours it will be assessed: the blood pressure, heart frequency, weight, signs of dehydration, plasma and urinary osmolality, plasma sodium. The test will be completed if more than 5% of weight is lost or if the patient presented tachycardia[2].

Short Desmopressin test is performed at the end of the dehydration test. DDAVP is administered – intranasal 20µg for children and 10µg infants and the urine will be collected every hour for 4 hours with and urinary osmolality will be measured[2].

This test will be useful to assess the capacity for maximum renal concentration and also to distinguish between central and nephrogenic diabetes insipidus.

HYPERNATREMIA

Hypernatremia is defined as total body water deficit relative to total body natrium content and it is present when plasma sodium is over 145 mmol/L[7].

Common causes are represented by: loss of water, as pure water loss (hypodipsia due to limited access of water or impaired thirst mechanism, diabetes insipidus, hypocalcemia) or net loss of hypotonic

fluids (renal – loop diuretics, osmotic diuretics, some intrinsic kidney diseases; gastrointestinal – vomiting, enterocutaneous fistulas, diarrhea; skin-burning, excessive sweating) and excess solute (hypertonic saline infusions, hyperaldosteronism)[3,7].

Hypernatremia of endocrine etiology is often due to: diabetes insipidus, 11 beta hydroxylase deficiency, mineralocorticoid receptor mutations (gain of function), epithelial sodium channel gene mutations, pseudo-hypoaldosteronism type 2 (Gordon syndrome) with augmented sodium reabsorption but normal aldosterone, primary hyperaldosteronism[3,7].

HYPONATREMIA

Hyponatremia is defined by excess total body water relative to total body natrium content and it is present when plasma sodium is under 135mEq/L[3,8].

Hyponatremia is classified depending on plasma osmolality in: hypotonic hyponatremia, isotonic hyponatremia and hypertonic hyponatremia.

Hypotonic hyponatremia (osmolality under 280 mOsm/kg H2O) has different causes, classified depending on plasma volume in: hypovolemic, euvolemic or hypervolemic. Hypovolemic hypotonic hyponatremia could be due to extrarenal sodium loss (urinary sodium under 20 mmol/l) – in diarrhea, emesis; 3rd sector losses – or due to renal sodium loss (urinary sodium over 20 mmol/l) – in tubulopathies, adrenal failure, isolated mineralocorticoid deficiency, definitive pseudo-hypoaldosteronism type 1, transient pseudo-hypoaldosteronism due to low expression of renal mineralocorticoid receptor in newborn[3,8,9]. Euvolemic hypotonic hyponatremia (urinary sodium over 20 mmol/l) is often associated with syndrome of inappropriate antidiuretic hormone secretion (SIADH) or cerebral salt wasting[3,8]. Hypervolemic hypotonic hyponatremia (urinary sodium under 20 mmol/l) is observed in cardiac or hepatic failure; nephrotic syndromes[3,8].

Isotonic hyponatremia (osmolality 280–295 mOsm/kg H_2O) is observed in hypertriglyceridemia, hyperproteinaemia[3,8].

Hypertonic hyponatremia (osmolality over 300 mOsm/kg H_2O) is associated with hyperglycaemia; hypertonic fluid administration[3,8].

Endocrine disorders with hyposodemia are: SIADH (hyper/euvolemic hypotonic hyponatremia); adrenal disorders, usually with hypovolemic hypotonic hyponatremia in 3β-hydroxysteroid dehydrogenase deficiency; 21 hydroxylase deficiency; aldosterone synthase mutations; pseudo-hypoaldosteronism type 1; renal disorders, such as Bartter syndromes, Gitelman syndrome[3,8]. SIADH is defined by water retention with plasma hypoosmolality – hyper/euvolemic hyponatremia but with normal value for AVP and abnormal for plasma osmolarity. SIADH is due to loss of inhibitory stimulus from the volume receptor system on pituitary, the main causes being pulmonary disorders– viral or bacterial infections; central nervous system disorders – infectious, metabolic; prematurity – with assisted ventilation; various therapies, such as vincristine. In each case with possible SIADH, it should be done a differential diagnosis, to exclude other causes of hypervolemic hyponatremia such as: renal failure, nephrotic syndrome, heart failure and cerebral salt losssyndrome.

CONCLUSIONS

The mechanism of water and sodium regulation is complex and the disorders associated with hyponatremia and hypernatremia have many etiologies, often rare in pediatric patients. Physiological neonatal resistance to aldosterone is an important observation especially in premature patients, due to lower expression of mineralocorticoid receptors, the treatment is concordant with this etiology. Because the kidney and adrenal are important regulators of water and sodium metabolism, the assessment in these disorders should include a careful renal evaluation (including natriuresis, urine culture and renal ultrasound) and hormonal adrenal sampling before any treatment.

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