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Severe hyponatremia in children: a review of the literature through instructive cases

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ABSTRACT

Hyponatremia is the most common electrolyte disorder in the pediatric population. Symptoms are related to the time in which hyponatremia has developed. The acute presentation could be dramatic, with neurological symptoms like headache, seizure, impaired mental status and even coma. It is essential for the physician to be aware of the possible causes of hyponatremia in the child in order to start a prompt treatment.

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KEY WORDS: Hyponatremia; Child; Water intoxication; Adrenal insufficiency.

Hyponatremia, defined as a serum sodium concentration below 135 mEq/L, is the most common electrolyte disorder observed in childhood.[1] Hyponatremia is classified according to the time of onset of the disorder in acute (<48 h) or chronic (>48 h).[2] Based on the serum sodium level, hyponatremia is defined as mild (130-135 mEq/L), moderate (125-130 mEq/L) or severe (<125 mEq/L). The main causes of hyponatremia are listed in Table I.[3, 4]

While acute severe hyponatremia is an emergency since it may cause brain oedema, chronic mild hyponatremia is also associated with increased morbidity and mortality.[5] Clinical presentation and subsequent management depend more on the rapidity with which sodium level decreases rather than the absolute value.[3]

Pathophysiological mechanisms

Serum osmolality refers to the concentration of different solutes in serum, with sodium being the most important. Hypertonicity is defined as serum osmolarity or tonicity >300 mOsm/kg, with normal values ranging between 285 and 300 mOsmol/kg.[6]

While hypernatremia always indicates hypertonicity, hyponatremia may be associated with low, normal or high tonicity.[7-9]

Water balance is achieved by ensuring an appropriate water intake, regulated by the thirst mechanism, and an adequate free water excretion by the kidneys, mediated by antidiuretic hormone (ADH) secretion.[10, 11] ADH is produced by specialized hypothalamic neurons (osmorecep-

TABLE I.—*Classification of hyponatremia based on extracellular fluid volume.*

Hypovolemia	Euvolemia	Hypervolemia
Extra-renal losses Gastrointestinal (emesis, diarrhea); skin (sweating or burns); third space losses (bowel obstruction, peritonitis, sepsis); primary adrenal insufficiency; cerebral salt wasting; third spacing. Renal losses Thiazide or loop diuretics osmotic diuresis; salt losing nephropaties.	Syndrome of inappropriate antidiuretic hormone secretion (SIADH); secondary adrenal insufficiency; hypothyroidism; high water/low solute intake (primary polydipsia/water intoxication).	Renal failure; heart failure; liver failure; nephrotic syndrome; hypoalbuminemia caused by gastrointestinal disease (protein-losing enteropathy).

tors), and its secretion is regulated by changes in serum osmolality levels.[12] When serum osmolality increases (normal values between 285 and 300 mOsmol/kg), ADH is released and causes the insertion of water channels into the membranes of cells lining the collecting ducts, allowing water reabsorption.[13, 14] Although to a lesser degree than osmolality, changes in blood volume and pressure may also regulate ADH secretion. Baroreceptors localized in the aorta and carotid arteries (high-pressure baroreceptors) and in the atria and pulmonary venous circulation (low-pressure baroreceptors), relay pressure and volume information.[10] These receptors are activated by an increase in blood volume and consequently inhibit ADH secretion or are stimulated when blood pressure falls, leading to ADH secretion. Renin, angiotensin, aldosterone and the sympathetic nervous system also participate in maintaining electrolyte concentrations in extracellular fluids.[15]

Clinical presentation

Clinical presentation varies according to the severity of hyponatremia and the rapidity by which sodium level decreases.[16] Symptoms do not usually appear until the serum sodium level drops below 120 mEq/L, but if sodium decreases rapidly, symptoms may occur earlier. When sodium levels drop quickly, water moves from the extracellular compartment to the intracellular space, in order to maintain osmotic balance. Patients develop neurologic symptoms resulting from cerebral oedema and endocrinal hypertension. Typical symptoms include a headache, nausea, vomiting, impaired mental status and progressive neurologic dysfunction with seizures and coma.[2, 7, 17] Children have a higher brain-to-skull size proportion meaning a minor space in which the cerebral tissue can swell, so neurologic symptoms can develop for higher value of serum sodium in children than in adults.[6, 18] However, if hyponatremia develops gradually, as in the case of chronic hyponatremia, neurological signs may be absent, due to the adaptation of the brain cells to extrude organic solutes from their cytoplasm, balancing intracellular to serum osmolality.[3, 19]

Diagnostic approach to hyponatremia

Clinical assessment is important in evaluating patients with hyponatremia, as etiology will guide clinical management. However, children with symptomatic hyponatremia may require a rapid correction of the serum sodium concentration, despite etiology.

Hyponatremia can be classified in hypotonic, isotonic and hypertonic depending on the serum osmolarity. Measuring the serum sodium and osmolarity is essential to distinguish between these conditions. Therefore, hypotonic hyponatremia may be classified according to the volume status in hypovolemic (volume depleted), hypervolemic (edematous) or euvolemic as listed in Table I.[3, 4] Clinical assessment of extracellular fluid volume (signs of hypo- and hypervolemia are listed in Table II), serum sodium, urinary sodium and fractional excretion of sodium (FENa) are needed to discriminate between these conditions.

TABLE II.—*Evaluation of patient's volume status.*
Signs of hypovolemia
Dry skin and mucous membranes
Tachycardia
Hypotension
Weight loss
Decreased urine output
Signs of hypervolemia
Raised jugular turgor
Peripheral edema
Pulmonary edema
Weight increase

Hypertonic hyponatremia

In the presence of high serum osmolality (serum osmolality >300 mOsmol/kg), as it may occur in hyperglycemia, fluid shift by an osmotic gradient from the intracellular to the extracellular compartment, diluting serum sodium levels (translocational hyponatremia). Once hyperglycemia has been corrected, serum sodium concentration will normalize.[3, 6, 20]

Isotonic hyponatremia

Pseudohyponatremia is a laboratory artefact consisting in false low measurements of sodium concentration along with normal osmolarity; this occurs when severe hypertriglyceridemia or proteinemia increases the solid phase of plasma, and the sodium concentration is measured using flame photometry or indirect ion-selective electrode assays.[6, 7]

Hypotonic hyponatremia

In the presence of low serum osmolality (<275 mOsmol/kg), hyponatremia may be classified according to the volume status in hypovolemic, hypervolemic or euvolemic.[3, 4] Beside the assessment of hydration status, evaluation of serum sodium, urinary sodium FENa can help guide the diagnosis (Figure 1).[6]

Hypovolemic hyponatremia

Hypovolemic hyponatremia is caused by a deficit in total body sodium and total body water (secondary to renal or extra-renal conditions), with sodium loss being much higher than water loss.[21] Extrarenal losses may occur secondary to gastrointestinal tract disorders (diarrhea, emesis)

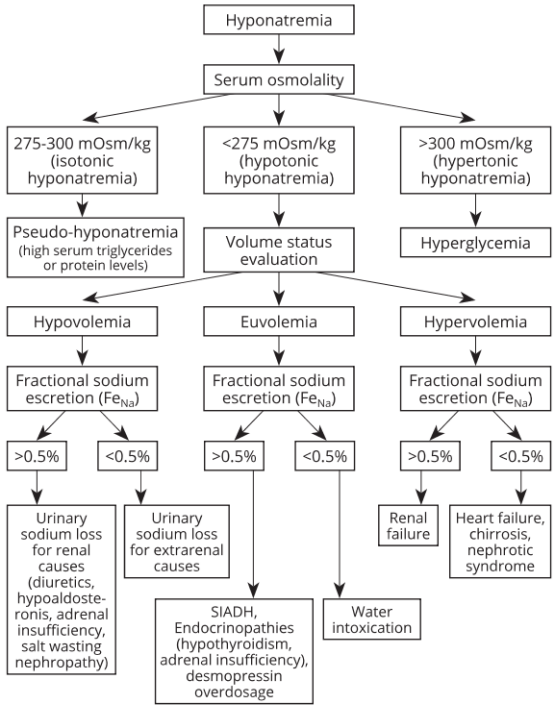

Figure 1.—Diagnostic assessment of hyponatremia. Modified from Zieg.[6]

or as a result of an isotonic fluid loss in the third space, through burns or for excessive sweating as in children with cystic fibrosis. Renal losses are mainly caused by several renal diseases (Table I). Renal causes of hypovolemic hyponatremia can usually be differentiated from extra renal causes by the history; the evaluation of the urine sodium level may also be helpful in differentiating the two conditions: urinary sodium level is low (<10 mEq/L) in patients with extra renal losses, since there is a renal response to maintain the intravascular volume. Patients with renal losses have high urinary sodium level, >20 mEq/L, secondary to an impaired renal response to volume loss.[22, 23]

Euvolemic hyponatremia

Patients with euvolemic hyponatremia have normal extracellular volume, low sodium loss and an increase in total body water, with no signs of pitting edema or ascites. The most common cause of euvolemic hyponatremia is the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Hyponatremia in SIADH is a

TABLE III.—*Diagnostic criteria and causes of SIADH.*

Diagnostic criteria of SIADH
(original criteria established by Bartter and Schwartz [Bartter])
Decreased serum osmolality (<275 mosm/kg)
Inappropriately concentrated urine (>100 mosm/kg)
Clinical euvolemia (secondary to regulatory adaptations)
Urinary sodium >40 mmol/L (secretion of atrial natriuretic peptide)
Normal thyroid and adrenal function
Etiology of SIADH
Malignant diseases
Carcinomas
Lymphomas
Sarcomas
Pulmonary disorders
Infections: bacterial and viral pneumonia, tuberculosis
Asthma
Cystic fibrosis
Central nervous system disorders
Infections: meningitis, encephalitis
Bleeding and masses
Medications
Drugs that stimulate release of AVP or enhance its action: SSRIs, tricyclic antidepressants narcotics, antipsychotic drugs, carbamazepine, cyclophosphamide
AVP analogues: desmopressin, oxytocin

result of excess water and is not primarily due to serum sodium deficiency. It is the combination of water retention together with a secondary solute loss, which results in reduction in serum sodium.[24] Hyponatremia is secondary to ADH secretion, which promotes renal water reabsorption, causing expansion of the extracellular volume. This activates secondary natriuretic mechanisms causing sodium and water loss and restoration of euvolemia.[25] Classification criteria and causes of SIADH are listed in Table III.[26]

Less frequent causes of euvolemic hyponatremia are endorinopathies (adrenal insufficiency and hypothyroidism) and psychogenic polydipsia.

Hypervolemic hyponatremia

In hypervolemic hyponatremia, there is an increase in both sodium level and total body water, with a relatively greater increase in water. This leads to a third space fluid loss, therefore a decrease in effective body volume resulting in a release of ADH, attempting to restore homoeostasis. Several edematous conditions, such as heart failure, cirrhosis and protein-losing enteropathy may cause hypervolemic hyponatremia.[17] Rarely hyponatremia occurs in nephrotic syndrome, whereas in these patients pseudo hyponatremia is much more frequently observed, due to the elevated concentrations of serum lipids.

Treatment

Management of hyponatremia is based on the etiology and presence or absence of symptoms. Acute severe hyponatremia usually is associated with neurologic symptoms such as seizures, poorly responsive to anticonvulsants. Symptomatic patients, regardless of the etiology, should be immediately treated because of the high risk of cerebral oedema and brain herniation.[27] Intravenous boluses of hypertonic saline (3% NaCl) should be administered: 2 mL/kg (maximum 100 mL) over 10 minutes, repeated as needed until symptoms subside. The goal is to increase serum sodium of 4-6 mEq/L in 1-2 hours.[28, 29] Hypertonic saline rapidly increases serum sodium, increasing extracellular osmolality and allowing water to move from the intracellular space to the extracellular space, decreasing cerebral oedema. In asymptomatic children, treatment should be based evaluating water excess or sodium deficiency, reducing fluid infusion in the first case and supplying sodium with isotonic saline in the second.[26] Fluid restriction is the mainstay in the treatment of asymptomatic SIADH.[30]

A rapid correction of serum sodium should be avoided, especially in children with chronic hyponatremia, as it can lead to central pontine myelinolysis or osmotic demyelination syndrome, due to brain cell dehydration.[31] Clinical presentation is characterized by gradual onset of neurological symptoms such as confusion, agitation and flaccid or spastic quadriparesis. Therefore, the increase in serum sodium concentration should not exceed 8-12 mEq/L over the first 24 hours,[2, 29] and this correction should be done even more cautiously in patients with chronic hyponatremia, by establishing a maximum correction limit at 4-8 mmol/L over a 24-hour period.[15]

Case presentation

Case 1

A 5-month-old infant was admitted to the emergency department with a three-week history of

mild weight loss (4% of the body weight, 6.45 kg at admission *vs.* 6.7 kg few days before the admission), poor feeding and inconstant recurrent vomiting; low-grade fever was associated in the last two days. His history was remarkable for congenital abnormality of the kidney and urinary tract (CAKUT). At the age of four months, his growth was regular, and routine blood tests showed increased serum creatinine 0.78 mg/dL, glomerular filtration rate 42 mL/min/1.73m^2, normal electrolytes and hemogasanalysis. On Emergency Department admission the patient appeared in good general conditions, eupneic, skin color appear normal, the capillary refill time was less of two seconds, blood pressure was 93/54 mmHg, cardio-thoracic and abdomen examination was unremarkable. Urinalysis tested positive for nitrites and leukocytes; microscope observation showed leukocyturia and bacteria. Laboratory tests showed 27.040/µL white blood cells (WBC), C-reactive protein (CRP) 6.36 mg/dL, serum creatinine 1.49 mg/dL, glomerular filtration rate of 17.5 mL/min/1,73m^2 and extreme hyponatremia (102 mEq/L), with hyperkalemia (5.8 mEq/L) and hypochloremia (68 mEq/L). Emogasanalysis showed metabolic acidosis (pH=7.21, pCO_2=21, BE=-7.7, HCO3=14). Fractional excretion of sodium (FENa) was 2.9% (n.v.<1%) and serum aldosterone was elevated (115.6 ng/dL; normal value 6.5-86 ng/dL).

Treatment with intravenous ceftriaxone was started along with a normal saline intravenous maintenance rate infusion. Feeding was unrestricted. After 48 hours of treatment, sodium level was 130 mEq/L, and the serum creatinine value was 0.79 mg/dL. Urine culture tested positive E. coli. A diagnosis of pseudohypoaldosteronism secondary to a urinary tract infection was made. The infant's general conditions remained stable, and he recovered uneventfully.

Case 2

A 2-year-old female was admitted for polydipsia and polyuria. At the age of one, gradually, she started to increase her water intake amounting to 2 liters/day. At the admission she appeared well hydrated, the weight was at the 25th percentile with no loss of weight in the previous months; the temperature was 36.4 °C, heart rate 102/minute, respiratory rate 21/minute, blood pressure: 90/62 mmHg. Her mucous membranes were wet. During admission, the baby frequently asked for water and if denied she became very irritable. Urine and blood electrolyte tests were in the normal range. A water deprivation test was performed. After 8 hours the test was stopped due the loss of weight of more than 5%, variation of serum osmolarity from 279 mOsm/L to 300 mOsm/L and urinary osmolarity from 231 mOsm/L to 357 mOsm/L. A partial central diabetes insipidus was suspected, and intranasal desmopressin therapy started at a dose of 5 mcg every 12 hours but, the day after, considering the persisting of the symptoms, the dose was increased at two puffs (10 mcg) in the morning. After few hours the baby began to be drowsy, and one hour later she had two episodes of projectile vomit and an episode of generalized seizures. Blood tests showed very low natremia (120 mEq/L) as a consequence of desmopressin overdosage. The child was moved to the intensive care unit, where she was treated with boluses of hypertonic saline solution (NaCl 3%, 2 mL/kg), followed by fluid restriction and the dose of desmopressin was reduced and switched to sublingual administration.

Case 3

An otherwise healthy 4-year-old girl was transferred to our hospital because of rapid onset of coma, preceded by vomiting and a tonic-clonic crisis. She had undergone appendicectomy six hours before. She never fully woke up from anesthesia and two hours after discharge from the operating theatre she had a biliary vomit and remained drowsy. In the following hours she had a tonic-clonic crisis and fell into a coma. Blood tests showed severe hyponatremia (Na 119 mEq/L, K 3.9mEq/L), a brain CT scan was reported as normal. On the admission to our hospital the patient was unresponsive, breathing spontaneously, apyretic, hypotonic with weak bilateral deep tendon reflexes, bilateral mydriasis with normal pupillary reactivity. Cardiac activity was regular with a heart rate of 72 bpm, there were no clinical signs of dehydration. Blood tests showed extremely low sodium levels (Na 116 mEq/l) and serum hyposmolarity (osmolarity 253.6 mOsm/L), with no other remarkable

abnormality (K 3.4 mEq/l, glucose 105 mg/dL, WBC 11.300/mmc, CRP 1.5 mg/dL, AST 50 U/dL, ALT 30 U/dL). Urine osmolarity was elevated (174 mOsm/L). A bolus of hypertonic saline solution (NaCl 3%, 2 mL/kg) was administered followed by fluid restriction (NaCl 0.9%, 900 mL/m^2/24 h). The patient rapidly improved, and she was responsive to pain stimuli after the first hour. She woke up completely four hours later (Na 126 mE/L). A Syndrome of Inappropriate Antidiuretic Hormone (SIADH) was diagnosed. Reviewing her clinical notes, it emerged that during and after surgery she received a 350 mL bolus plus her full fluid maintenance with a hypotonic solution (NaCl 23 mEq/L, K 20 mEq/L, glucose 5%, at a rate of 1800 mL/m^2/24 h).

Case 4

A 12-year-old boy was referred from a local hospital for a history of fatigue and malaise associated with hyponatremia (Na: 121 mEq/L). His past history was remarkable for a previous hospital admission two weeks earlier: after an episode of repeated vomiting with syncope, hyponatremia (124 mEq/L) was found. Several investigations (blood and urine lab tests, abdominal ultrasound, brain MRI, electroencephalogram, chest X-ray) had tested negative. Hyponatremia was corrected by mean of a normal saline infusion; gastroenteritis was suspected, and the boy was discharged. The evening before admission he had felt unusually thirsty, and he reported drinking at least 2 liters of water. The day of admission he vomited a few times and presented marked asthenia with dizziness on standing. No diarrhea or change in weight was reported. Urinary output was described as normal. Physical examination and vital signs were unremarkable; however, hyperpigmentation of the skin and the gums was noted. On admission laboratory tests showed hyponatremia (121 mEq/L), hypochloremia (86 mEq/L), hyperkaliemia (5.91 mEq/L), elevated sodium renal loss (NaU 163 mEq/L, KU 48 mEq/L, ClU 119 mEq/L), low serum osmolarity (248 mOsm/kg) and high urinary osmolarity (896 mOsm/L). Glucose blood and urinary levels were normal without ketosis as were blood count and blood gas analysis. Recurrent hyponatremia with elevated sodium renal loss, clinical signs (fatigue, dizziness, vomit and tanned skin) normal renal function was suspected of adrenal insufficiency: relatively low levels of cortisol (7.95 mcg/dL; n.v. 6.2-19.4) considering the stress the boy was under and marked ACTH elevation (>1250 pg/mL) was found. Elevated levels of renin (>500 mUI/mL) and low values of aldosterone (3.1 ng/dL) confirmed a diagnosis of adrenal insufficiency.

Case 5

A 5-year-old male child affected by autism spectrum disorder was admitted to the emergency department for the sudden onset of a generalized epileptic state, characterized by right eyes deviation and tonic contraction of the four limbs, in the absence of fever. There was no history of previous seizures, and he was not taking any therapy. On admission, a dose of 0.1 mg/kg midazolam, 0.1 mg/kg of lorazepam and 20 mg/kg of phenytoin was administered intravenously sequentially without obtaining a remission of the epileptic state. Blood analyses showed hyponatremia (119 mEq/L) in the absence of other electrolyte disorders; blood gas analysis and glycaemia were normal. Giving the fact that the epileptic state was caused by the hyponatremia, two hypertonic saline (3% NaCl) bolus of 2 mL/kg were administered, obtaining a serum sodium value of 125 mEq/L and the resolution of the seizures. Patient's vital signs always remain normal in the next hours, and urinary catheterization revealed an initial polyuria (15 mL/kg/hour) with diluted urine (specific gravity of 1000) that progressively resolved.

On direct questioning, the parents reported that the child, from three weeks, had developed an obsession for the water (drinking more of 4 liters of water daily) that was very similar to other obsessions presented in the past (the need to drink a bottle of coke when he saw one, the need to tear paper all the time). They also informed us that lately the oppositional behavior of the child worsened, so they often offer water, even in large amount, to calm him.

A normal value of serum sodium was reached in 24 hours so normal saline (0.9% NaCl) infusion was stopped, and oral intake of water was limited to 1.5 L/day (the maintenance for the

patient with a weight of 20 kg). Glucocorticoid insufficiency and hypothyroidism were excluded through hormonal blood dosages.

A diagnosis of symptomatic hyponatremia as the consequence of psychogenic polydipsia was made. The patient started treatment with risperidone. Fractioning the total daily amount of water in bottles of 100 mL helped to decrease the child request of water.

Discussion

Urinary tract infection (UTI) in newborn has nonspecific symptoms such as poor feeding and weight loss, even in the absence of fever. In renal failure, nephrons are not able to increase excretion of augmented acid product and infection may worsen the renal function with an inadequate compensation and metabolic acidosis. Infants younger than six months of age with urologic malformations and concomitant urinary tract infection may develop secondary pseudohypoaldosteronism.[32] Pathogenesis is probably a result of high intrarenal pressure, inflammation and immaturity of the tubular function leading to tubular resistance to aldosterone. The major symptoms are the failure to thrive, poor weight gain and dehydration. In case 1 urinary electrolyte levels on admission showed significant sodium losses even with a very low natremia. Renal infection played a major role since hyponatremia was not present in the previous controls before infection, neither recurred after UTI treatment.

In case 2 a diagnosis of partial central diabetes insipidus was made; considering high sensitivity to desmopressin acetate and partial defect of incretion, an inadequate dose of intranasal desmopressin was the cause of the excess of water. Therefore, hyponatremia is a known side effect of desmopressin overdosage. Intranasal drug assimilation is unpredictable and therefore not recommended: desmopressin acetate therapy is usually prescribed under form of sublingual tablets.[33]

In case 3 hyponatremia was an iatrogenic condition, due to inadequate fluid therapy in children with high risk to develop SIADH. Inflammation, surgery and pain play a fundamental role in triggering ADH incretion. Hypotonic solutions should never be used for maintenance fluid therapy; patients in critical conditions are at particularly high risk of developing SIADH.[34]

In case 4 cortisol deficiency decreased cardiac output and vascular tone. Moreover, catecholamines decreased inotropic and pressure effects were causing orthostatic hypotension that potentially could have been progressed to shock. Aldosterone deficiency resulted in hyponatremia and hyperkalemia decreasing sodium reabsorption and potassium excretion in the distal nephron. In adrenal insufficiency hyperkalemia tends to occur later, hypoglycemia and ketosis are not always present, while and cutaneous hyperpigmentation can be overlooked at clinical examination. For this reason, the initial presentation can mimic SIADH. In this case, an SIADH-syndrome seemed unlikely due to the presence of syncope and dizziness on standing as presenting signs, increased thirst, the absence of weight increase and normal urinary output. In any case of hyponatremia with high urinary sodium and osmolality, adrenal insufficiency should be seriously considered, as the onset is frequent without the full typical picture.[35] Misdiagnosis of SIADH in adrenal insufficiency may have very serious consequences: fluid restriction without glucose infusion and delayed steroid administration may severely worsen an adrenal crisis and even be life threatening.

In case 5, hyponatremia was caused by water intoxication. The only ingestion of water is an occasional cause of hyponatremia because healthy kidneys can expel a high volume of diluted urine. However, more than 0.8-1 Liter of water per hour can cause hyponatremia in an adult patient; this means that a rapid amount of water could result in symptomatic hyponatremia.[6, 18] The risk is higher in infants whose renal function is not entirely mature, so they have a limited capacity to eliminate the excess of water. In literature, there are several cases of water intoxication as a consequence of child abuse or diluted infant formula.[18, 36, 37] Psychogenic polydipsia is especially described in schizophrenic patients.[38, 39] As known, impaired social skills, repetitive behavior and limited interests are the features of autism spectrum disorder.[40] Difficulties in the communication compromised empathy, and sensory overburden could often result in aggressive

or oppositional behavior towards caregivers and is not uncommon for caregivers to find a strategy to cope with these conducts. Therefore, water intoxication in this kind of pediatric population could be the consequence of a restricted interest toward drinking and the parent's attempt to calm the child down with water. A study by Terai *et al.* reported a more severe drinking behavior in children with autism than in other patients with mental retardation.[41]

Conclusions

In conclusion, hyponatremia is a quite common condition in hospitalized patients. Serious disorders of sodium balance may cause severe and permanent brain injury if not properly recognized and treated. A detailed history and accurate physical examination, along with appropriate laboratory examinations should lead to a correct diagnosis, therefore to proper management.

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