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THE ROLE OF HYPOTHYROIDISM IN THE ETIOLOGY OF HYPONATREMIA - CASE REPORT AND A SHORT REVIEW

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ABSTRACT

Hyponatremia induced by hypothyroidism is a rare phenomenon and a correlation between them can be argued only with possible mechanisms. Hyponatremia often results from the concomitant development of several overlapping pathological events. The association between hypothyroidism and hyponatremia should be considered only if explanations for any other etiological causes have been exhausted. We present the case of a female patient aged 67 years who has previously undergone surgery for a meningioma and who presented with symptoms such as nausea, biliary vomiting, headache and epigastric pain. Laboratory results indicated multiple electrolyte imbalances, including hyponatremia, but the brain imaging studies did not confirm cerebral edema or the presence of tumor development. Under electrolytic correction treatment which was supplemented with L-thyroxine, the biochemical parameters were corrected and normalized and the patient was relieved of her symptoms. This case thus raises the possibility that hyponatremia could be induced or at least precipitated by hypothyroidism. Thyroid dysfunction tests should be targeted in cases of hyponatremia with non-specific causes, even if hypothyroidism is rarely the cause.

Keywords: hyponatremia, hypothyroidism, L-thyroxine, thyroid, TSH

Introduction

Hypothyroidism begins when the thyroid gland no longer produces enough thyroid hormones. Several causes could trigger this disease: hypothyroidism may appear as a consequence of primary gland deficiency or inadequate thyroid gland stimulation by the hypothalamus or pituitary gland. Central causes of hypothyroidism often produce other manifestations of hypothalamic or pituitary dysfunction and are defined by inappropriately or low levels of thyroid stimulating hormone (TSH) relative to deficient thyroid hormones (1).

Uncommon causes which should not be neglected are autoimmune ones. The immune system protects the body from various invading agents; in autoimmune diseases there is a possibility of confusing enzymes and cells, and subsequently the immune system can attack them. If this is the case, there may be abnormalities in both cell-mediated immunity and humoral immunity.

Hashimoto's thyroiditis is one of the most common forms of autoimmune thyroiditis characterized by an inflammatory condition of the thyroid gland, triggered by genetic variants that support sensitivity and environmental factors. There is a possibility that patients suffering from an autoimmune disease may further develop

other autoimmune diseases. At the same time, in the current worldwide pandemic state of Coronavirus disease of 2019 (COVID-19), the question of autoimmunity and disease risk was raised, in many cases the phenomena of familial clustering being observed: a study from 2020 which involved approximately 50000 patients concluded that autoimmune diseases may in fact be a risk factor for any respiratory infections, including (but not specific for) COVID-19 (as opposed to liver diseases which were associated with more devere forms of this disease). The association of at least three autoimmune diseases in the same individual defines multiple autoimmune syndrome. At least one of the diseases associated with multiple autoimmune syndrome is a skin disease such as herpetiform dermatitis, vitiligo, psoriasis, systemic lupus erythematosus or alopecia areata (2). Other autoimmune diseases that have high incidence and can be associated are: ulcerative colitis, polymyositis, rheumatoid arthritis, scleroderma, idiopathic thrombocytopenic purpura, lichen sclerosus (3, 4) .

Multiple autoimmune syndrome comprises at least three different autoimmune diseases. Careful monitoring of patients with a history of autoimmune disease is necessary because there is the rick of later developing a new autoimmune disease. The signs and symptoms of hypothyroidism are, but not limited to, dry skin, cold intolerance, constipation, slow thinking, weight gain, thick skin, swelling, slowed heart rate and delayed relaxation of the ankle reflexes. Symptoms often have an insidious onset and overlap significantly with patients with thyroid disease and with those without. Many signs and symptoms of thyroid dysfunction are neither specific nor sensitive. For example, the signs and symptoms associated with hypothyroidism, such as dry skin, fatigue and constipation, could have other causes (5). Other symptoms such as hyporeflexia, ataxia, dysdiadochokinesia, digitalagnosis should be differentiated from vitamin E deficiency.

Among thyroid disorders, hypothyroidism was the most common cause involved in the onset of serum hyponatremia. Hyponatremia can occur secondary to an untreated manifestation of hypothyroidism, namely, myxedema. Hypothyroidism associated with adrenal insufficiency, inadequate secretion of antidiuretic hormone (SIADH) and primary polydipsia may be included in the differential diagnosis of hyponatremia. Hypothyroid hyponatremia develops as a result of the inability to excrete free water caused by both excessive secretion of vasopressin and a reduction in the amount of water in the distal nephron. The reduction in renal perfusion may be due to a deficiency of thyroid hormones that may have a systemic effect on peripheral vascular resistance and cardiac output. In clinical practice, hyponatremia associated with hypothyroidism is frequently exacerbated in patients who associate additional comorbidities, confounding factors. In this case, hyponatraemia is more likely to develop than hypothyroidism, however, differential investigation and diagnosis with glucocorticoid deficiency and inadequate section of antidiuretic hormone is needed (6, 7).

In medical practice, hyponatremia is the most common electrolyte disorder. It is defined by low serum sodium concentration. The etiological classification includes 4 categories: pseudohyponatremia (low sodium concentration being given by hyperlipidemia, hyperglycemia, hyperproteinemia), hypovolemia (loss of fluid through vomiting, diarrhea, diuretic), hypervolemia (fluid retention, cardiac insufficiency), renal insufficiency (inappropriate antidiuretic hormone secretion syndrome, adrenal insufficiency, hypothyroidism) (7, 8). The association of hyponatremia with hypothyroidism tends to be weak, so that there are minor (more statistical than clinical) differences between the groups of patients with euthyroidism and hyperthyroidism who have hyponatremia (9, 10) . The level of TSH does not correlate with serum sodium

Concentrations (11-13); however, this fact cannot be rejected unless other causes of hyponatremia are identified and thyroid dysfunction tests indicate overt hypothyroidism.

Case presentation

Clinical findings and disease course

A 67 years-old woman, who previously suffered from a meningioma which was surgically removed approximately 2 years

prior, is currently presenting with nausea, biliary vomiting, epigastric pain and headache, symptoms which developed two days ago. The patient denied smoking, alcohol consumption, drugs or any digestive system pathology. The patient was normotensive. Although the day after hospitalization the symptoms of nausea and vomiting persisted, a slight improvement with anti-emetics was obtained, and the patient could consume water, but not solid foods. After a few hours, her condition worsened: drowsiness and poor response to pain stimuli were observed. The neurological examination did not reveal the presence of focal neurological signs, but anisocoria was present.

Differential diagnosis

The factors that contributed to the patient's worsening condition were dehydration and hypotension, both due to vomiting and probably precipitated by a tumor recurrence in the brain (an assumption made prior to the cerebral computer tomography (CT) examination). The most probable metabolic causes were considered to be hypoglycemia due to the low intake of food and the frequent vomiting, and also hypothyroidism-induced hyponatremia.

Investigations

Initially, the serum glucose level was 58 mg/dl and after 5% glucose administration, it returned to the normal limits (interval range (IR) of 70-105 mg/dl), but the patient's condition did not improve. Multiple electrolyte disturbances have been identified: hyponatremia 110 mmol/L (IR: 136-145 mm/L), hypochloremia 73,8 mmol/L (IR: 98 - 107 mmol/L), hypokalaemia 2,3 mmol/L (IR: 3,5 - 5.1 mmol/L), metabolic alkalosis with bicarbonate levels of 36 mmol/L (IR: 22-29 mmol/L), TSH - 20 mIU/L (IR: 0.27-4.20 mIU/L), free T4 - 0.237 ng/dl (IR: 0.82-1.77 ng/dl), free T3 - 2,6 ng/ml (IR: 2.21-4.43 ng/ml, adrenocorticotropic hormone (ACTH) - 21 pg/ml (IR: 7.2-63.3 pg/ml), luteinizing hormone (LH) – 15 mIU/ml (IR: 7.7-58.5 mIU/ml), (follicle-stimulating hormone) FSH – 50 mIU/ml (IR: 25.8-134.8 mIU/ml). The serum osmolarity was 245 mOsm/kg. On the electrocardiogram the findings indicated a first degree atrio-ventricular block without any other specific changes. The cranio-cerebral CT scan, thyroid ultrasonography and chest x-ray did not identify pathological changes, while the abdominal ultrasonography revealed a septate gallbladder with deposits found in the lower third of the gland.

Treatment

Electrolyte deficiency correction was performed with hypertonic saline solution of 5,85% with 2 ml/kg and potassium saline solution of 7,4%; hemodynamic stabilization was done with the help of isotonic saline solution. The increase in serum sodium concentrations in the first 24 hours was negligible, but, after the administration of 25 μg of L-thyroxine, an increase of 9 mmol/L was registered (with improved patient status), and subsequent increases of 5 and, respectively, 6 mmol/L, each in the following 2 days. The normalization of the natremia serum levels was reached on the third day.

Outcome and follow-up

Improvement of the patient's condition was observed when the hyponatremia was corrected and normal serum levels were reached. Administration of L-thyroxine favored the patient's response to the hypertonic saline solution treatment, whom hardly remembered the prior events. On the fourth day of hospital admission, the symptoms that were still persistent were headache and nausea, which resolved the following day.

Review of case reports

Our review of the medical literature revealed several cases of hyponatremia that have been reported in patients suffering from hypothyroidism. Hypothyroidism-induced hyponatremia seemed to be the direct effect of L-thyroxine treatment interruption. Life-threatening hyponatremia can be found in patients with hypothyroidism, who underwent a total thyroidectomy or even after radioactive iodine therapy done for thyroid cancer. The symptomatic hyponatremia responded to intravenous hypertonic saline solution associated with thyroid hormone replacement, the patients making a full recovery. In conclusion, in the setting of symptom overlap regarding hyponatremia and the neurological expressions of hypothyroidism, it is an essential step in correct

patient management to evaluate hypothyroid patients for possible hyponatremia and to apply proper treatment in order to avoid long-term complications of chronic hyponatremia (14-18).

Discussions

Although hypothyroidism-induced hyponatremia tends to be euvolemic, adrenal insufficiency should be considered in cases of hypovolemia (19). Since our patient had a history of meningioma, we excluded a secondary adenohypopituitarism by measuring serum levels of ACTH, LH and FSH which were in the normal ranges. At the same time, this patient has elevated TSH levels with low free-T4, indicating a primary dysfunction of the thyroid gland. The existence of a digestive system disorder which could explain the fluid loss in the context of hyponatremia and hypothyroidism symptom overlap, may contribute to the installation of hypovolemic hyponatremia. With a TSH level of under 50 mIU/L, some authors suggest that hyponatremia could not be induced exclusively by hypothyroidism, and other possible causes should be identified (20).

The mechanisms by which hypothyroidism could trigger hyponatremia are not yet understood. In the case of chronic hypothyroidism, the excretion of water occurs due to the high level of antidiuretic hormone initiated by the decrease of the cardiac output which stimulates the carotid sinus baroreceptors. This occurs though in more severe cases of hypothyroidism (21). Acute hypothyroidism is commonly seen in patients with thyroid cancer who stop thyroid treatment due to the radioactive iodine therapy that they will go through. The glomerular filtration rate decrease can be implied in this context as a complementary mechanism of action (22, 23). Hypothyroidism can induce changes in the kidney such as: decreases in the glomerular filtration rate and structural and functional impairment (electrolytic pumps) in the kidney (24). In children with primary hypothyroidism a decrease in renal parenchyma and an increased prevalence of urological abnormalities have been observed (25).

Hemodynamic changes in hypothyroidism involve the vascular muscle and are manifested by decreasing their tone and reactivity to vasodilators and vasoconstrictors. A study of euthyroid, hyperthyroid and hypothyroid rats revealed that nitric oxide synthase is ultimately decreased in the aorta, veins, and renal cortex (26).

The initiation of hyponatremia treatment should be done in accordance with the severity, duration and triggers of this state. Depending on the serum sodium concentrations, hyponatremia is classified as: mild - 130-135 mmol/L, moderate - 125-129 mmol/L and severe <125 mmol/L (27). In order to avoid osmolar demyelination syndrome (ODS) literature data suggest that in cases of chronic hyponatremia, a correction of 4-8 mm/L per day should be made if the risk for ODS development is high, and a maximum correction of 10-12 mmol/L in the following days, if the risk ODS is low. In acute hyponatremia, an emergency correction of 4-6 mmol/L is required in order to prevent cerebral hernia and ischemia (28). The onset of ODS following hyponatremia treatment could be determined by the development of hypotonic protective mechanisms in the brain. Initially, the excess water is directed to the cerebrospinal fluid, then it is dispersed in the systemic circulation. In the following hours, intracellular depletion of sodium, potassium and chlorine takes place until a plateau is reached, after which the cerebrospinal fluid plays the role of electrolyte supplier.

The late adaptation mechanism (in chronic hyponatremia) ensures the involvement of organic osmolites in tonic regulation. They represent amino acids and derivatives, polyols, sugars, methylamines, methylsulfonium compounds and urea. Osmolites can maintain a relatively constant water level in the brain, in spite of low electrolyte concentrations (29). The rapid correction of hyponatremia in such cases determines astrocyte death by inducing intracellular protein aggregation and by exerting stress on the endoplasmic reticulum. In addition to chronic hyponatremia and instant correction, the increased risk of developing ODS con be also the result of cofactors such as: liver disease, malnutrition or alcoholism (30, 31).

Treatment of euvolemic hyponatremia with vaptans (vasopressin receptor antagonists) may be initiated if hypothyroidism and adrenal

insufficiency have been excluded and if hyponatremia is not hypovolemic, namely it has not resulted from fluid loss. Vasopressin receptor antagonists are effective in chronic and/or hypervolemic hyponatremia (cirrhosis, congestive heart failure) by normalizing serum natrium concentrations and by improving hemodynamics, but long-term administration appears to have no positive effects on mortality rates (32, 33). In chronic hyponatremia sodium saline solution will be used along with water restriction measures (34).

The patient's symptoms corelate with the severity of hyponatremia. The possibility of its inducement by the digestive disorder is real in the context of fluid loss. The septate gallbladder identified by abdominal ultrasonography could have served as a triggering factor, but this is a congenital anomaly from which the patient has not experienced discomfort previously, the pain developing after the consumption of certain types of food. The patient's epigastric pain could be explained by the multiple episodes of vomiting.

Conclusions

The presented clinical case supports the fact that hyponatremia can be induced, or, at least precipitated by, hypothyroidism, despite the fact that the medical literature and numerous studies do not provide evidence of a strong connection between these entities. At the same time, thyroid dysfunction tests should be targeted in cases of hyponatremia of unspecified causes, even if hypothyroidism is rarely the cause.

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Availability of data and materials

The information generated and analyzed during the current study is available from the corresponding author on reasonable request.

Ethics approval and consent to participate

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Patient consent for publication

The patients provided written informed consent for the publication of any associated data and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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