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SOUNDING BOARD

The Controversies of Hyponatraemia in Hypothyroidism

Weighing the evidence

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الاختلافات في تقييم نقص صوديوم الدم عند قصور الغدة الدرقية

تقييم الأدلة

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ABSTRACT: Hyponatraemia is a common electrolyte disturbance, with moderate (serum sodium: 125–129 mmol/L) to severe (serum sodium: ≤125 mmol/L) forms of the disease occurring in 4–15% of hospitalised patients. While it is relatively common, determining the underlying cause of this condition can be challenging and may require extensive laboratory investigations. To this end, it is important to ascertain the efficacy of laboratory tests in determining the cause of hyponatraemia. Up to 10% of patients with hypothyroidism also have hyponatraemia. Routine evaluation of thyroid function is often advocated in cases of low serum sodium. A review and discussion of the available literature is presented here to examine this recommendation.

Keywords: Causality; Kidney Disease; Hypothyroidism; Hyponatremia.

الملخص: نقص صوديوم الدم هو اضطراب أيوني شائع لحالات مرضية تتراوح بين المعتدلة (الصوديوم في الدم: 129–125≤ مليمول/لتر) إلى الحادة (الصوديوم في الدم: 125≤ مليمول/لتر) تحدث في 15%–4 من المرضى المنومين في الستشفيات. مع أنه شائع نسبيا، فإن تحديد سبب هذا الاعتلال يشكل تحديا وربما يحتاج لفحوص مخبرية واسعة النطاق. تحقيقا لهذه الغاية، فإن من المهم التأكد غالبا من فعالية الفحوصات المعملية في تحديد سبب نقص صوديوم الدم. إن ما يصل إلى 10% من المرضى الذين يعانون من قصور الغدة الدرقية لديهم أيضا نقص صوديوم الدم. ولذلك فإن التقييم الروتيني لوظيفة الغدة الدرقية في حالات انخفاض الصوديوم في الدم مطلوب. هنا نقدم عرضا ومناقشة للأدبيات المتوفرة لدراسة هذه التوصية.

مفتاح الكلمات: السببية؛ أمراض الكلى؛ قصور الغدة الدرقية؛ نقص صوديوم الدم.

Hyponatraemia is a common electrolyte abnormality, but distinguishing its underlying cause(s) is usually challenging, and extensive laboratory investigations are commonly applied.[1–6] Excluding hypothyroidism in patients with unexplained hyponatraemia has been widely attempted, but the strength of such a link has not been clearly defined and is, at times, downplayed.[7–9] Although 10% of patients with hypothyroidism also have hyponatraemia, clinicians often ignore its clinical significance.[1] When hyponatraemia and hypothyroidism are found to coexist, the former is not necessarily a consequence of the latter, and other causes of low sodium (Na) concentrations should still be investigated.[7,8,10] In a patient with a marked decline of Na levels and an undetermined thyroid status, clinicians must consider an evaluation of thyroid function in the patient's work-up.[10] The implication of changes in natraemia status in hypothyroidism has yet to be fully elucidated. In spite of this, an absolute link between hypothyroidism and Na levels is included in standard internal medicine and subspecialty textbooks. However, such an association should be reaffirmed through individual testing.[11–14]

Cost-Effective Medicine: *Recent medical practice*

A recent review suggested that about half of the most common clinical scenarios in daily practice include unnecessary testing and diagnostic approaches.[15] This review documented 146 contemporary medical practices that have subsequently been reconsidered over the past 10 years. Investigators assessed 1,344 original articles that studied a novel medical practice or tested a conventional one. Only 27% of the articles verified an established and tested practice. Of the articles that tested current medical practice, 40.2% of these practices were found to be ineffective. An additional 38% endorsed the importance of an existing

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practice while 21.8% were unconvincing.[15,16] In fact, some of the most commonly utilised tests did show some beneficial evidence in previously published reports.[17] However, a careful analysis of the gathered data and its clinical significance from the Cochrane Database in 2004 and 2011 showed insufficient evidence for the necessity of these practices, revealing that they were adding more of a load to already overburdened healthcare systems.[17]

Non-Thyroidal Illness Syndrome

Some acute and chronic medical conditions are associated with a common biochemical derangement of thyroid function, known as non-thyroidal illness syndrome (NTIS). This condition is a common cause of medical costs in the absence of a causal intrinsic thyroid sickness.[18] Studies assessing morbidity and mortality rates in NTIS subjects treated with thyroid hormones revealed no statistically significant findings.[18,19] These studies found there was no need for specific therapeutic interventions, such as the administration of thyroid hormones, in patients with various forms of NTIS in the context of concurrent systemic illness.[18,19] This explains, in part, the futility of routine thyroid testing in hyponatraemic patients in whom thyroid aberrancy can be misleading. Routine testing of the thyroid in hyponatraemic patients is based upon little evidence and results in unnecessary testing and follow-ups for sick euthyroid patients.[18,19]

THE ROLE OF VASOPRESSIN

The most noticeable peculiarity in clinically significant hyponatraemia is its pathogenesis, which remains highly debatable. In general, hypothyroidism has been associated with increased total body Na, proposing the vital role of water retention.[6] Regardless of the Na levels in hypothyroid states, diminished and/or delayed free water load excretion and impaired renal dilution capacity are paramount, pointing towards a possible role for vasopressin or antidiuretic hormone (ADH) and the need for effective water excretion. However, such a correlation in patients with hypothyroidism is weak. In hypothyroidism, hyponatraemia seems to be associated only with the severest cases of myxoedema where impaired cardiac function causes baroreceptor-mediated vasopressin secretion and total body water retention.[20] In fact, the impaired excretion of water load in hypothyroidism has been demonstrated in several studies and it has been suggested that inappropriate secretion of ADH might mediate water retention.[13,20]

Elevated vasopressin levels in patients with hypothyroidism have been described in a variety of reports, yet the findings were inconsistent.[12,21–23] Previous studies have demonstrated that in rats with hypothyroidism, there is no upregulation of hypothalamic vasopressin gene expression; therefore the reduction in cardiac output and glomerular filtration rate (GFR) observed in severe hypothyroidism may be due to non-osmotic stimuli to vasopressin release.[21,22] In 20 patients with myxoedema, raised plasma vasopressin concentrations were observed in cases of mild hyponatraemia (Na levels of 130–142 mmol/L).[23] Surprisingly, after a water challenge, 75% of the studied individuals did not show a complete decline in elevated vasopressin concentrations and only 10% had a suppressible vasopressin response. This signifies the coexistence of an intrinsic renal mechanism unrelated to the vasopressin itself.[12,23] After the achievement of euthyroidism, evaluations of urinary excretion and vasopressin inhibition were satisfactory following the oral water load.[23]

The expected osmotic trigger in patients with hypothyroidism seems to be normal. A study by Iwasaki *et al*. assessed eight patients with uncontrolled myxoedema due to primary hypothyroidism after infusing them with 5% hypertonic saline.[21] After the saline infusion, severe primary hypothyroidism was observed in all patients without a convincing suppression of the measured high vasopressin levels.[12,21] Despite the findings of additional osmotic triggering mechanisms, rising plasma osmolality and a consequent rise in measured vasopressin levels was sufficient in the entire patient group and mild hyponatraemia was observed in only two patients.[21] Plasma vasopressin was appropriately suppressed in each case during water loading.[21] These outcomes show that an inappropriate rise in plasma vasopressin is not common in myxoedema and that compromised water elimination is predominantly due to vasopressin-independent mechanisms. This results in impaired water excretion and urine concentrations even when plasma osmolality is low, which is possibly a sequel to associated hypervolaemia.[12,24]

NON-VASOPRESSIN-RELATED MECHANISMS

Intrinsic Renal Mechanisms

Reduced effective renal plasma flow and diminished proximal tubule Na reabsorption have also been implicated in the pathophysiology of hypothyroidism.[22,25,26] In severe cases, the effective arterial blood volume can decrease sufficiently to stimulate arginine vasopressin (AVP) secretion via baroreceptor mechanisms. Additionally, the impaired cardiac function that often occurs with advanced myxoedema can lead to an elevation in plasma AVP levels. In

severe cases, hyponatraemia can occur secondary to thyroxine (T)3 deficiency, affecting renal Na tubular reabsorption.[1,10,12,27] Different factors influence Na handling and T3 levels in adult populations, including diet, alcohol consumption, hypertension and renal status.[12] Hyponatraemia and hypothyroidism have been found to coincide in a small number of selected populations.[7,14]

ROLE OF CELLULAR LOW SODIUM/ POTASSIUM PUMP EXPRESSION AND INTERSTITIAL DEPOSITION

The Na/potassium (K) adenosine triphosphatase (ATPase) enzyme exchange process is the metabolic pacemaker of thyroid hormone-responsive tissues, leading to an increase in Na pump activity.[28] Either directly at the messenger ribonucleic acid transcriptional level or through intermediate cellular and ionic regulators, thyroid hormones play an essential role in regulating the complex homeostatic regulation of ATPase activity in the cell. Na/K/ATPase activity is higher in euthyroid states.[12,28] Reduced Na/K/ATPase enzymatic activity and impaired Na/hydrogen exchange activity of the proximal tubular borders and other specific segments, as part of a decline in cell metabolism in hypothyroid conditions, can contribute to the diminished proximal tubular capacity for Na reabsorption in hypothyroidism.[12,22]

Another probable influence contributing to hyponatraemia in hypothyroidism is the accumulation of interstitial mucopolysaccharides resulting in mutual solute and fluid retention, diminishing effective tissue perfusion and local lymphatic drainage, particularly in myxoedema.[20] In hypothyroidism, hyponatraemia seems to be associated only with the severest cases of myxoedema as impaired cardiac function causes baroreceptor-mediated vasopressin secretion and total body water retention.[20] Furthermore, total body sodium is increased, evident from isotopic studies, and it is likely that the excess Na is bound to the mucinous material present in the connective tissue.[29] In addition, the impaired excretion of water load has been demonstrated in several studies and it has been suggested that inappropriate secretion of ADH might mediate water retention.[13,20]

ROLE OF HYPOTHYROIDISM TYPE IN ADULTS

Apart from myxoedema or complete hypopituitarism, primary hypothyroidism as the principal cause of hyponatraemia in either hospitalised or ambulatory patients remains questionable.[13,30] Reports from studies conducted on congenital hypothyroidism and adults with primary hypothyroidism did not show a definitive connection between hyponatraemia and hypothyroidism, even with a concomitant decline in the GFR among hypothyroid patients.[31,32] Serum creatinine levels could be elevated in patients with uncomplicated hypothyroidism without a significant decrease in serum Na levels.[32]

Despite previous reports describing hypothyroidism as a secondary cause of hyponatraemia, the evidence for such an association is poor.[1] This was shown in recent studies of either congenital hypothyroidism, iatrogenic ablated cases or adults with primary hypothyroidism; all of these attempted to eliminate the influence of comorbid conditions by addressing a correlation between thyroid-stimulating hormone (TSH) and Na levels and demonstrate a significant change in Na concentrations as a result of normalising the hypothyroid state.[14] Such associations were inconclusive due to the small study populations and the presence of other confounders, together with differences in Na handling mechanisms.[1,14] Moreover, when hyponatraemia accompanies hypopituitarism, secondary hypothyroidism is generally a sign of secondary glucocorticoid insufficiency rather than hypothyroidism itself.[12]

CONGENITAL HYPOTHYROIDISM

When hyponatraemia is detected in congenital hypothyroid cases, a lack of thyroid hormones is not the chief influencing factor.[13,14,20,28–36] In a study conducted by Asami *et al*., no cases of hyponatraemia were found in 32 congenital hypothyroid neonates where serum Na concentrations did not statistically differ from those of 16 control neonates (median sodium level: 139 mmol/L).[31] Furthermore, no association was found between the measured thyroid functions and serum Na. Moreover, two months after thyroid hormone replacement, serum Na levels in the infants had not changed significantly.[31] In this study, the elimination of previously postulated factors that can affect Na handling in paediatric populations, such as malnutrition, acute gastroenteritis, renal tubular disorders and syndrome of inappropriate ADH secretion, did not confirm the claimed direct hyponatraemia-hypothyroidism link.[31] This finding suggests other possible causes should be investigated.[31,37,38]

Further Data and Related Mechanisms from Inpatient and Outpatient Settings

Studies involving larger numbers of patients found that serum Na values were comparable in subjects with raised TSH values.[10,14] However, laboratory data included hospitalised patients with raised TSH values

due to non-thyroidal illnesses such as acute hepatitis, nephrotic syndrome and depression.[10,14] Again, the data showed an absence of a clinically applicable relationship between newly diagnosed hypothyroidism and hyponatraemia.[10,14] Moreover, looking exclusively at serum samples of newly diagnosed hypothyroid patients in ambulatory settings showed a statistically significant relationship between lower Na concentration in a small number of individuals and hypothyroidism; however, the relationship showed no clinically significant importance.[33] It has been found that hyponatraemia was more common in patients with impaired renal function at diagnosis (serum creatinine concentrations of >1.1 mg/dL) than in those with normal renal function, which is another condition that can contribute to the progression of hyponatraemia in hypothyroid cases.[32]

A study involving 33,912 patients in a large urban general hospital showed matched serum Na levels in euthyroid patients and hypothyroid patients (TSH >40 U/L; n = 445; Na = 138.6 mmol/L). There was no significant difference between the euthyroid subjects (11.4%) and the hypothyroid subjects (12.8%) with regards to the proportion of patients with serum Na lying below the reference interval of 135 mmol/L.[14]

A small retrospective case series studied 10 otherwise healthy ambulatory patients with primary hypothyroidism. These patients had a median TSH level of 193 μU/mL (range: 104.2–515.6 μU/mL; normal range: 0.40–5.50 μU/mL) and a median Na level of 138 mmol/L (range: 136–142 mmol/L; normal range: 135–146 mmol/L).[11] The lowest Na level was 136 mmol/L with a concurrent TSH level of 469.7 μU/ml. No single patient was found to have a Na level lower than 135 mmol/L.[11] This observation suggests that hypothyroidism alone is less likely to contribute to hyponatraemia.

A study conducted in an outpatient setting among individuals with hypothyroidism found that for every increase of 10 mU/L of TSH, there was a fall of only 0.14 mmol/L in the subjects' Na concentrations.[33] Thus, the elevation of TSH required for a clinically substantial fall in Na to occur was considerable. Again, none of the hypothyroid subjects and only two of the control patients had Na values of <120 mmol/L. However, a relationship between lower Na concentrations and hypothyroid status was statistically significant, yet unlikely to be of clinical significance.[33]

Another retrospective study included 128 thyroid-ablated patients with differentiated thyroid cancers who were not receiving thyroid hormone replacement. A mean TSH level of 130.3 mU/L and a serum Na level of 139.3 mmol/L was observed in hypothyroid cases. Findings confirmed the infrequency of hyponatraemia in uncontrolled hypothyroidism; despite the observed elevated serum creatinine levels, there was no significant biochemically detected hyponatraemia.[32]

In a retrospective review of emergency room records including more than 9,000 patients, hyponatraemia was significantly more common in patients with high TSH levels than the normal TSH control group (<15% versus 9%, respectively; P <0.01).[10] Although serum Na did not show a significant correlation with TSH and free T4 levels, a significant correlation was seen between free T3 levels and serum Na levels. Even though such a borderline correlation did exist, no proven practical electrolyte disturbances were confirmed.[10] While there may appear to be an association between thyroid function and electrolyte disorders, it is most likely that clinically-related electrolyte derangements, such as hyponatraemia, are only established in extreme hypothyroid states.

Most patients with hyponatraemia have one evident cause, but there may be other contributory factors. Real volume reduction can be initiated by the loss of Na and water, leading to decreased tissue perfusion and provoking ADH secretion. This response is facilitated by carotid sinus-related baroreceptors.[20] As a consequence, water retention and hyponatraemia can develop with the depletion of effective arterial blood volume. Because hypothyroidism and hyponatraemia are common findings in hospitalised patients, their co-occurrence may not necessarily be causal; therefore, other justifications for hyponatraemia should be pursued unless hypothyroidism is severe.[8,10,13] A patient may not have any symptoms that indicate a thyroid illness that warrants further thyroid testing. However, an unexplained reduction in the plasma Na concentration might inspire physicians to carry out further thyroid testing.

Recommendations

Overall, there is no strong evidence that supports routine thyroid testing for hyponatraemia in either hospital or outpatient encounters as compared to the general population. A history of concurrent illness and a medications list, as well as a careful physical examination, may provide clues to the pathogenesis of hyponatraemia. Hyponatraemia in hypothyroidism cannot be ignored, but the clinical relevance of this association is questionable. TSH levels should be determined in challenging cases of hyponatraemia where both vasopressin-mediated and intra-renal mechanisms may be involved in the pathogenesis of the condition. Thyroid assays should be ordered only when severe hypothyroidism is suspected in order to avoid unnecessary testing.

Conclusion

Thyroid function tests are a simple and rapid way of obtaining a satisfactory diagnosis for suspected hypothyroidism. When a patient presents with typical symptoms, the diagnosis usually does not require a complex or invasive clinical investigation. Although included in many diagnostic algorithms, hypothyroidism very rarely causes hyponatraemia. Hyponatraemia is not a disease in and of itself, but a spectrum of diseases and/or adverse medication effects, making it a worthy clinical challenge. Hypothyroidism is a possible aetiology, yet other probable causes of hyponatraemia should be sought first. The authors of this report conclude that there is no compelling evidence that suggests the need for routine thyroid testing in hyponatraemia. A thorough physical examination together with a history of the patient's concurrent illnesses and their current medications should assist in identifying the cause of hyponatraemia. The current era of medicine demands the elimination of unnecessary testing. Therefore, to avoid unessential assessments, thyroid testing should only be performed in particularly challenging cases of hyponatraemia or in possible cases of profound hypothyroidism.

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