Case report

Hyponatraemia and hyperpigmentation in primary adrenal insufficiency

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SUMMARY

Hyponatraemia is a common electrolyte disturbance with multiple causes. We present a case of a 49-year-old Caucasian female with cholangiocarcinoma, who had a hyponatraemia which was initially assumed to be based on a syndrome of inappropriate antidiuretic hormone secretion as paraneoplastic phenomenon. At physical examination, hyperpigmentation was seen and multiple episodes with syncope were reported. Subsequent endocrine assessment with a synthetic adrenocorticotropic hormone (ACTH) stimulation test and measurement of ACTH levels revealed primary adrenal insufficiency also known as Morbus Addison. We started hydrocortisone and fludrocortisone replacement therapy, resulting in resolving of symptoms, hyponatraemia and hyperpigmentation.

BACKGROUND

Hyponatraemia is a common clinical problem with a multifactorial aetiology. The general incidence of hyponatraemia (serum sodium <136 mEq/L) in hospitalised patients is 30% and in 2.6% serum sodium is <124 mEq/L.1 One of the causes of hyponatraemia is hypocortisolism. Early recognition of this disease is of vital importance, because hypocortisolism is a potentially life threatening condition and presenting symptoms are often non-specific.

Figure 1 Skin hyperpigmentation of a Caucasian female.

The first diagnostic steps in hyponatraemia are to confirm a hypo-osmolar hyponatraemia using serum osmolality, this measurement should match the calculated osmolality. Urinary osmolality is also necessary and measures ADH activity, which is present when urinary osmolality ≥100 mOs/kg. Urinary sodium can help determine if sodium loss is renal or non-renal. The use of diuretics should always be considered, as it makes urinary sodium and osmolality more difficult to interpret.

After confirming a hypotonic (serum osmolality <275 mOsm/kg) hyponatraemia, in absence of ADH activity, the differential diagnosis includes primary polydipsia, tea and toast and beer drinkers hyponatraemia. If urinary osmolality ≥100 mOsm/kg, urinary sodium and assessment of a patients’ volume status are needed.2

A hyponatraemia with a low urinary sodium (<30 mmol/L) and a hypovolaemic state can be the result of vomiting, diarrhoea, sequestration of fluid and recently stopped diuretics. If the patient is hypervolaemic, cardiac failure, liver cirrhosis and nephrotic syndrome needs to be considered.

Hyponatraemia with a high urinary sodium (≥30 mmol/L) and a hypovolaemic state can also be the result of vomiting, but also the use of diuretics or primary adrenal insufficiency. If the patient is
euvoalaemic secondary adrenal insufficiency and SIADH need to be considered.

In case of hyponatraemia without hypotonicity, other conditions should be considered. This can be the result of a hyperglycaemia or exogenous solute (ie, mannitol, intravenous immune globulines). In these situations, water is drawn from intracellular to the extracellular space, resulting in a lowered serum sodium concentration, but hypotonicity. Another consideration is a pseudohyponatraemia, which is a laboratory miscalculation of the serum sodium. This phenomena can be hyperlipidaemia, hyperproteinemia or obstructive jaundice. The electrolyte concentration is measured in plasma, which normally consists of about 93 percent water and seven percent solids, mostly proteins and fats. The serum sodium concentration is determined based on the measured plasma sodium concentration and the estimated percentage of water. An increase in solids leads to a lower water percentage, and therefore a miscalculation of the serum sodium, however toxicity remains normal.2

In this article, we present a case of hyponatraemia and hyperpigmentation caused by a Morbus Addison in a patient with jaundice caused by a pancreatic carcinoma. Initially, it was interpreted as SIADH, but hyperpigmentation was the vital clue in diagnosing primary hypocortisolism.

CASE PRESENTATION

A 49-year-old Caucasian woman with a medical history of auto-immune hyperthyroidism was hospitalised for analysis of painless jaundice under suspicion of a cholangiocarcinoma. At presentation, she had a hyponotic hyponatraemia (serum sodium 124 mmol/L, measured serum osmolality 235 mOsm/kg, calculated serum osmolality 260.3 mOsm/kg) combined with a urine osmolality of 678 mOsm/kg and a urine sodium of 219 mmol/L. Awaiting further diagnostics (eg, morning serum cortisol, thyroid-stimulating hormone and thyroxine) she was initially assessed as euvoalaemic, leading to a different diagnosis of SIADH. In daily practice, SIADH is often assumed to be the cause of hyponatraemia, even before the diagnostic work-up is completed. This was also the case in our patient, in whom treatment for SIADH was initiated before the adrenal insufficiency was adequately ruled out. Recent guidelines also state that a SIADH diagnosis requires exclusion of other possible causes of hyponatraemia, like adrenal insufficiency.5 In our case, the assumed diagnosis SIADH resulted in delay in the final diagnosis.

DIFFERENTIAL DIAGNOSIS

Our patient had a hyponotic hyponatraemia (serum sodium 124 mmol/L, serum osmolality 255 mOsm/kg, calculated serum osmolality 260.3 mOsm/kg) combined with a urinary osmolality of 678 mOsm/kg and a urinary sodium of 219 mmol/L. Pseudohyponatraemia, for example as a result of jaundice, was excluded as cause because the hyponatraemia was hyponotic hyponatraemia.

She was initially assessed as euvoalaemic, leading to a differential diagnosis of SIADH. In daily practice, SIADH is often assumed to be the cause of hyponatraemia, even before the diagnostic work-up is completed. This was also the case in our patient, in whom treatment for SIADH was initiated before the adrenal insufficiency was adequately ruled out. Recent guidelines also state that a SIADH diagnosis requires exclusion of other possible causes of hyponatraemia, like adrenal insufficiency.7 In our case, the assumed diagnosis SIADH resulted in delay in the final diagnosis.

TREATMENT

Our patient had both an auto-immune hyperthyroidism and a Morbus Addison and was diagnosed with a polyglandular autoimmune syndrome type 2.4 We started cortisol replacement treatment with hydrocortisone 50 mg intravenous once, followed by oral hydrocortisone 20 mg–10 mg–10 mg per day. The dose was doubled because of simultaneous use of rifampicine. We also started fludrocortisone 62.5 µg per day. This treatment was indicated because in our patient, there was a primary cause of adrenal insufficiency. Therefore, mineral corticosteroid is also lacking and substitution is essential.

OUTCOME AND FOLLOW-UP

Our patient was treated for her adrenal insufficiency resulting in full recovery of symptoms and a normalisation of hyponatraemia in 4 days. Also, within 2 weeks the hyperpigmentation resolved (figure 2).

Analysis for the jaundice of our patient initially led to the suspicion of cholangiocarcinoma, but histological examination revealed pancreatic adenocarcinoma. She underwent a pancreaticoduodenectomy. The operation was, unfortunately, complicated by intra-abdominal bile acid leakage treated with a temporary percutaneous biliary stent. Unfortunately, during oncological follow-up metastasis and later also local recurrence of the pancreatic carcinoma were diagnosed, therefore palliative chemotherapy was given, despite this effort our patient deceased 2 years after diagnosis.

DISCUSSION

In this article, we present a case of hyponatraemia and hypervolvement caused by Morbus Addison in a patient with jaundice as a result of pancreatic carcinoma. Morbus Addison is a rare disease, and pancreatic carcinoma occurring simultaneously is, to our knowledge, never reported before. It did result in an inappropriate initial diagnosis, as SIADH is a common finding in patients with malignancies. We did find a case of a woman with autoimmune polyglandular syndrome type 2 having the combination of hyponatraemia, hypervolvement caused by Morbus Addison with a previous autoimmune Hashimoto’s thyroiditis.5 In our case, undersubstitution of levothyroxine could have contributed to the hyponatraemia, however, thyroid hormone concentration was normal with a levothyroxine dose of 100 µg/day.


Reminder of important clinical lesson

**INVESTIGATIONS**

To confirm our hypothesis of primary adrenal insufficiency, we performed a synthetic adrenocorticotropic hormone (ACTH) stimulation test (synacthen 250 µg) showing a cortisol decrease from 217 nmol/L to 207 nmol/L at 30 minutes. Basal plasma ACTH level was 492 pmol/L (normal range 0–11 pmol/L) and adrenal auto-antibodies were positive. Serum renin concentration was 1520 µU/mL (normal range 3–60 µU/mL) whereas serum aldosteron was not detectable (<50 pmol/L). These results confirmed the diagnosis of Morbus Addison. Abdominal CT-scan, performed in the diagnostic process of the suspected cholangiocarcinoma, showed no abnormalities of the adrenal glands.
Hyponatraemia in patients with hypocortisolism is due to aldosterone deficiency, leading to renal sodium loss, and is enhanced by water retention via an increased release of antidiuretic hormone (ADH) in response to a reduction in systemic blood pressure and cardiac output caused by cortisol deficiency. The ADH response is maintained by cortisol deficiency because the direct negative feedback of cortisol on ADH release is declined. This explains why in hypocortisolism hyponatraemia does not improve with only fluid restriction.

Hyperpigmentation in primary adrenal insufficiency is caused by an increased production of α-melanocyte-stimulating-hormone (αMSH). Both αMSH and ACTH originate from the pro-hormone peptide pro-opiomelanocortin (POMC). In primary adrenal insufficiency POMC production is strongly increased in response to the fall in cortisol levels with concomitant release of αMSH causing a bronze hyperpigmentation.

Early recognition of Morbus Addison is of vital importance, because hypocortisolism can be a life threatening condition in case of physical stress as activation of the hypothalamic-pituitary-adrenal axis is an essential response during illness. Furthermore, Morbus Addison often presents with non-specific symptoms, which makes hyperpigmentation an important clue in the diagnosis.4

Learning points

► Hyponatraemia can be the first presentation of Morbus Addison.
► In patients with hyponatraemia and co-morbidity predisposing to SIADH, adrenal insufficiency should always be considered as contributory factor or primary cause.
► Hyperpigmentation caused by increased production of α-melanocyte-stimulating-hormone can be a vital clue to consider primary hypocortisolism, also when other serious co-morbidity is present.
► Hyperpigmentation in this case of Morbus Addison resolved within 2 weeks after starting cortisol replacement therapy.

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