

Relapsing Syndrome of Inappropriate Antidiuretic Hormone Production Responding to Tolvaptan Treatment in a Patient With a Micronodular Formation of the Posterior Pituitary Gland



Summary

The syndrome of inappropriate ADH-secretion (SIADH) is a common cause of low sodium levels with diverse aetiology. Here, we report a case of a 41 years old male patient diagnosed with SIADH and a good response to Tolvaptan therapy. Of interest, as a potential unique cause, magnetic resonance imaging revealed a micronodular structure in the posterior pituitary, while no other common cause of SIADH could be identified. Hence, to the best of our knowledge, this is the first case of a Tolvaptan-responsive SIADH associated with a pituitary micronodular structure.

Background

The syndrome of inadequate secretion of antidiuretic hormone (ADH) is a common cause of low sodium levels. There are three major aetiologies: 1. paraneoplastic conditions with ectopic hormone production, 2. increased production of ADH in the hypothalamus and secretion into the pituitary gland induced by systemic pathologies like infections, trauma, medication, pulmonary disease or neurologic pathology and 3. traumatic injury of the pituitary, e. g., due to neurosurgery. In the case of the latter, SIADH is often transient and may be followed by a diabetes insipidus due to the destruction of the posterior pituitary. It is important to exclude other causes for hyponatremia before the diagnosis of SIADH is made [1].

Mechanistically, ADH, also named arginine vasopressin (AVP), is produced in the hypothalamic nuclei supraopticus and paraventricularis and secreted into blood from axonal endings in the posterior pituitary. Regulation is made by osmotic and pressure-receptor. The AVP-receptors V1 and V2 are located in vessels and kidneys and affects vasoconstriction and water restriction, and thereby, low sodium levels [1]. Disorders of increased ADH secretion lead to hyponatremia causing unspecific symptoms and neurologic failure. After diagnosis, sodium level must adjusted carefully because of the risk for osmotic demyelination syndrome [2].

Case-presentation

A 41-year-old male Caucasian presented with persistent abdominal pain since the previous day at our emergency department of the University Medical Center, Schleswig-Holstein. He reported some dizziness and an upset stomach. At that time, the patient had a history of alcohol abuse. He resided in an assisted living environment and had no history of any regular medication.

He had a medical history of hospitalization due to hyponatremia the month before the current admission. Then sodium levels normalized after balancing fluid homeostasis. Two months earlier, he had undergone surgery with colonic resection and ostomy after colon perforation and peritonitis due to a para-rectal abscess. The procedure was complicated by septic shock and ventilation therapy at intensive care unit (ICU) was required.

Clinical examination at the current admission showed a patient with the reduced general condition and post-surgery malnutrition (weight: 50.5 kg, height: 171 cm, BMI: 17.8 kg/m²). He reported light pressure pain in the lower abdomen. The neurologic examination was clinically unremarkable. There was no clinical evidence of infection or trauma at that time.

Investigation

Point of care laboratory testing showed a sodium of 110 mmol/l, indicating biochemical severe hyponatremia while having clinically moderate symptoms.

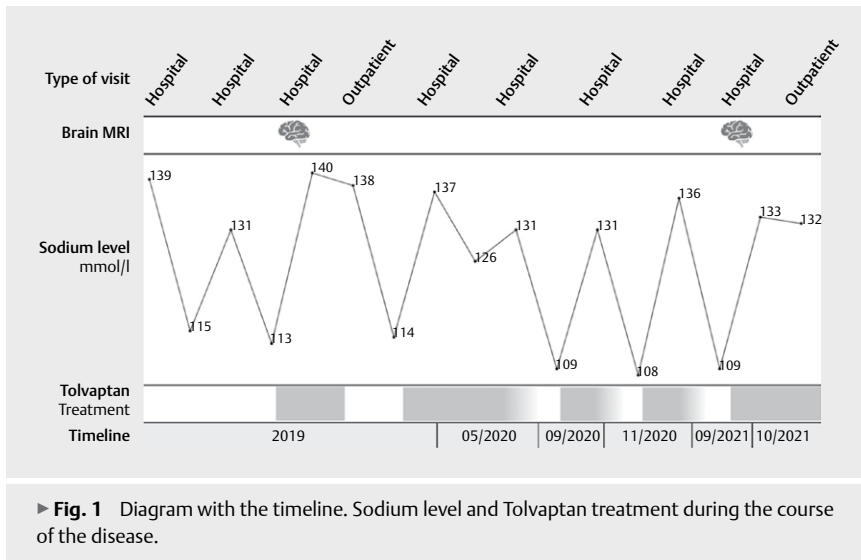
Vital signs were unremarkable (breathing rate: 16/min, temperature: 36.2 °C, heart rate: 64/min, oxygen-saturation: 99%, GCS: 15) except for a blood-pressure of 160/100 mmHg. Electrocardiogram showed no abnormalities.

A standard-laboratory workup for differential diagnoses of hyponatremia was done. Essential criteria for SIADH had been fulfilled: plasma-osmolality was 253 mOsmol/kg indicating hypotonic hyponatremia. Hy-

dration status was assessed clinically and by ultrasound ruling out hypervolemia. Urine analyses showed increased urine-sodium (110 mmol/l) and urine-osmolality (389 mOsmol/kg). There was no history of diuretics in medication. Renal function testing was normal (creatinine: 50 µmol/l). Testing of thyroid hormones showed a mild reduction of fT3 at the time of admission, most likely in terms of a low-T3 syndrome (TSH: 3.36 mIU/l, fT3: 3.58 pmol/l, fT4: 14.9 pmol/l). Repeated testing of thyroid hormones afterwards revealed concentrations within the normal range. Basal cortisol concentrations were in the normal range with 141 nmol/l.

After the diagnosis of SIADH, a possible aetiology was investigated. There was no evidence of tumour indicating ectopic production. No malignancies had been found in computed tomography-scans of the thorax and abdomen. Ultrasound of the testis showed no lesions or evidence of seminoma. AFP and beta-HCG were in the normal range. There had been no signs of infection with normal CRP (2.62 mg/l), PCT (<0.05 µg/l), clinical examination and pulmonary X-ray.

For differential diagnoses of possible central neurological diseases as a cause of SIADH, a brain magnetic resonance imaging (MRI) was performed. Of interest, while common neurological causes of a SIADH could be excluded, a 3 mm × 6 mm T2-hyperintense lesion in the posterior pituitary was found. An experienced neuroradiologist classified this lesion as a micronodular formulation. Despite this structure, no signal for the posterior pituitary gland was recognizable (► Fig. 1a, b). Further measurements of pituitary hormones revealed a mildly increased prolactin (20.6 µg/l [ref. 4.0–15.2 µg/l]) and normal concentrations of insulin-like growth factor-1 (132.0 µg/L [ref. 58–219]). Total testosterone (8.3 µg/l [ref. 2.5–8.4]) was also in the normal range but with increased levels for SHBG (144 nmol/l [ref. 18.3–54.1]), thereby the free testosterone was calculated to be 203 pmol/l [ref. >243]. Luteinizing hormone (LH) and fol-



luteal stimulating hormone (FSH) were in the normal range (LH: 4.9 U/l [ref. 1.7–8.6], FSH: 6.5 U/l [ref. 1.5–12.4]), thus indicating mild normogonadotropic hypogonadism.

Treatment

In ICU, the patient was stabilised by sodium chloride (NaCl) infusions and fluid management. After slowly elevating sodium levels into the lower normal range, fluid restriction was recommended for stabilisation of serum NaCl concentrations. However, sodium levels tended to decrease very rapidly and therefore, Tolvaptan 7.5 mg per day was introduced under close control of electrolytes. Fortunately, the targeted therapy with a final dose of 15 mg Tolvaptan resulted in the stabilisation of sodium levels and complete clinical recovery. No clinical signs of central osmotic demyelination syndrome occurred.

Outcome and follow-up

The patient was discharged from the hospital and scheduled to be followed-up in the outpatient centre at the Division of Endocrinology, Diabetes and Clinical Nutrition. Tolvaptan medication was increased to 15 mg per day. No clinical signs of a transition to central diabetes insipidus (CDI) developed. One month after discharge from the hospital and sustained sodium serum concentrations, an attempt was made to reduce Tolvaptan treatment and switch to fluid restriction under regular control by

the primary care physician. However, some days later the patient was readmitted to hospital with symptomatic hyponatremia (Na: 114 mmol/l) and Tolvaptan medication was re-initiated followed by normalisation of sodium level.

Over the last two years, the patient showed very poor compliance regarding the Tolvaptan medication and was admitted to our hospital several times with hyponatremia following Tolvaptan termination. Each time Tolvaptan therapy was re-started, sodium levels normalized (► **Fig. 2**).

The follow-up MRI of the pituitary gland showed constant findings (► **Fig 1c, d**).

Following the German guidelines for hormone-inactive microadenoma, the wait and watch strategy was implemented. With stable disease and good response to therapy, no neurosurgery was recommended; therefore, no histopathology was achieved. After significantly improving the compliance by repetitive educational interventions of the patient and his legal representative, the patient is now adherent and in good condition.

Discussion

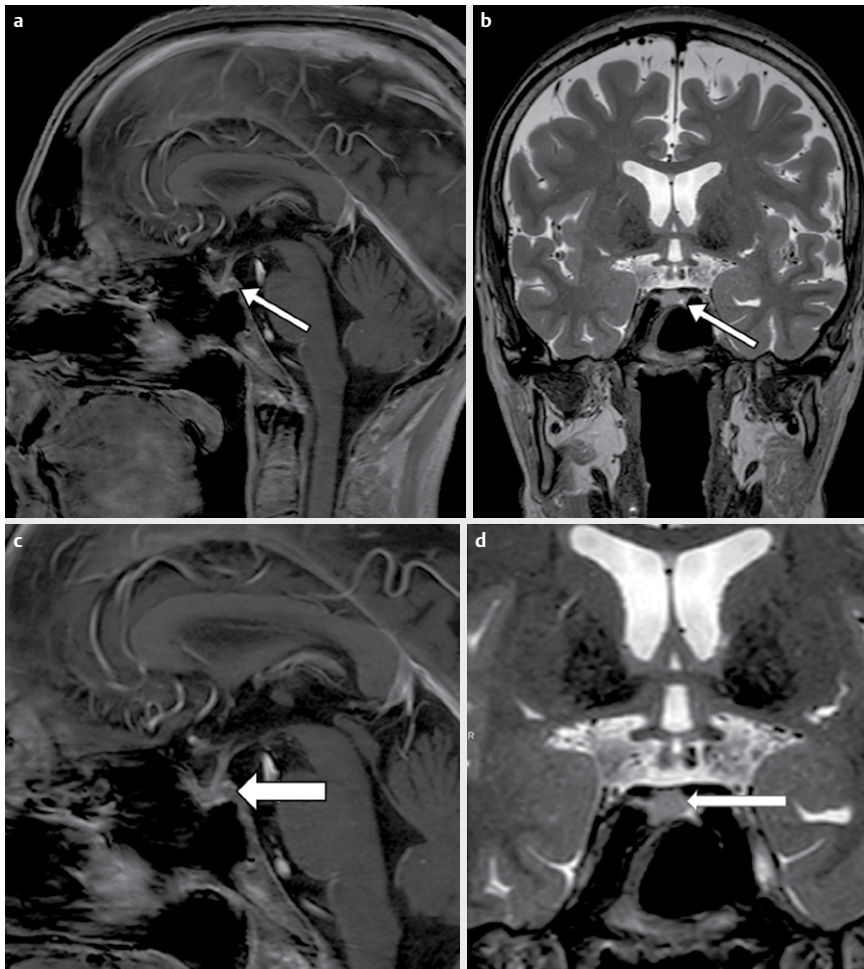
Here, we present a case of SIADH associated with a micronodular structure of the posterior pituitary with relapsing hyponatremia responding to Tolvaptan therapy. The workup of hyponatremia and SIADH as

a common cause is a frequent clinical problem; however, the present case suggests a rather uncommon cause giving insights into the mechanism of SIADH.

There are two important possible mechanisms of SIADH: ectopic secretion vs. stimulation of hypothalamic ADH-producing cells. In this case, imaging revealed no malignancy, ruling out ectopic ADH production. An occult malignancy was highly unlikely due to the long-term follow-up of more than 2 years now. Hence, there was no sign of chronic (more than 2 years) systemic condition to cause SIADH.

Therefore, the micronodular structure of the posterior pituitary, as a remarkable finding, might have led to ADH overproduction. There are only a few reports of hormone-producing adenoma in the posterior pituitary, mostly ACTH-producing, but none are known to produce ADH [3]. Cases of SIADH due to a macroadenoma of the pituitary and cure after surgery have been described [3–5]. In addition, a case of SIADH after pituitary apoplexy is also reported [6]. In the absence of histopathologic or laboratory evidence of hormone production, mechanical stimulus leading to ADH production is suspected in these cases. The finding of hyponatremia due to SIADH after hypothalamic surgery also suggests a mechanical stimulus. In the present case with microadenoma and no compression of the pituitary stalk, a different mechanism must be suggested. In vitro and in vivo secretion of AVP is stimulated by different neurotransmitters. The precise pathways and their clinical significance are not known yet. [7, 8] In our patient, a stimulation by neurotransmitters produced by the adenoma would be conclusive and explain the clinical presentation. However, the exact mechanism is difficult to approach without any invasive procedure.

Although being described as a marker for ADH production, we did not test for copeptin in this clinical case because it is not recommended in clinical guidelines due to its poor specificity in distinguishing SIADH from other causes of hyponatremia [9–11]. While measuring copeptin repeatedly in a constant ambulance setting would be scientifically interesting, we did not perform



► **Fig. 2** Magnetic resonance imaging (MRI) imaging (10/2019). The MR study was performed using a 3 T MRI (Phillips Healthcare). Brain MR imaging shows a bright nodule in the posterior part of the hypophysis in thin coronal T2-weighted sequences (a, magnification in c). In sagittal T1 post-gadolinium-enhanced sequences obtained directly after the bolus injection, the formation can be identified as a relatively non-enhancing lesion within an intensely enhancing pituitary gland (b, magnification in d).

such testing due to the underlying compliance problems.

Transition into central diabetes insipidus is often reported subsequent to SIADH in case of traumatic injury, e. g., due to neurosurgical intervention. In this case, no diabetes insipidus evolved, most likely due to the constant stimulation by the microadenoma and the absence of cell destruction as described after surgery or apoplexy [9].

At first admission to our hospital, the patient reported a history of alcohol abuse. While acute ingestion is associated with ADH suppression, chronic alcohol consumption can lead to an increase in ADH levels, mirroring SIADH. As a result, hyponatremia may be present in approximately 17% of subjects

with chronic alcohol-use disorder [12]. While we cannot rule out chronic alcohol abuse as a potentiating factor in the present case, our patient did not show any withdrawal symptoms at any visit to our hospital and did also not show other laboratory findings often associated with chronic alcohol abuse, e. g. no hypertriglyceridemia (0.8 mmol/l [ref. <2.31]), normal glutamate-oxalacetate transaminase (39.2 U/l [ref. <50]), normal glutamate-pyruvate transaminase (26.1 U/l [ref. <50]), normal gamma-glutamyltransferase (GGT) (53 U/l [ref. <60]). In addition, a drug screen was performed four times at the different admissions during the last 2 years, whereby three times no alcohol was detectable; only once, in May 2020, we measured 1.67 o/oo. These findings suggest acute but not chronic alcohol abuse. We fa-

voured GGT as an equal or slightly more sensitive marker of alcohol abuse than the also described carbohydrate-deficient transferrin (CDT) [13–15]. Furthermore, CDT is shown to be more specific in ruling out chronic alcohol consumption, whereas GGT seems to have strength as an indicator for organ damage, which was our main goal in the reported case [14].

Hence, while we do not have a histopathological examination as proof of ADH release of the microadenoma, from our point of view, it is unlikely that chronic alcohol abuse is the most likely cause of SIADH in the present case.

One also has to discuss our choice of therapy algorithm chosen: following German guidelines, “wait and see” is recommended for microadenomas with no proof of hormone production. Surgery as therapy for macroadenoma is accompanied by a risk of pituitary hypothyroidism, adrenal dysfunction and gonadal failure. In addition, in this case surgery of the posterior pituitary gland most likely might result in central diabetes insipidus, especially since no normal signal of the posterior gland was detectable in the MRI. Since no morphological change could be documented over a time period of 24 months, we therefore decided on a watch-and-wait strategy and long-term Tolvaptan therapy in the present unique case.

In conclusion, we describe a case of SIADH associated with a micronodular structure of the posterior pituitary gland suggesting new mechanistic insight into this rare aetiology of ADH overproduction.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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