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Hyponatraemia – diagnostic difficulties in 2.5-year-old boy with nephrogenic syndrome of inappropriate antidiuresis. Case report

Hiponatremia – trudności diagnostyczne na podstawie opisu przypadku 2,5-letniego chłopca z nerkopochodnym zespołem nieadekwatnej antydiurezy

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Abstract

Normal sodium levels in the extracellular fluid are in the range of 135–145 mmol/L. Low serum sodium (hyponatraemia) is a common water and electrolyte balance disorder. Dehydration and overhydration are the most common causes of hyponatraemia in children. This paper describes a case of a 2.5-year-old boy admitted to the paediatric ward due to pneumonia. The child showed reluctance to fluid intake, hypoosmolar hyponatraemia with hypouricaemia, and increased urinary sodium excretion in the absence of abnormalities in hydration status. He had a family history of persistent hyponatraemia and hypertension in his grandfather. After excluding pituitary, thyroid, adrenal cortex pathologies, kidney disfunction, and proliferative processes in the differential diagnosis, cerebral salt wasting syndrome, the syndrome of inappropriate secretion of antidiuretic hormone and the renal-related syndrome of inappropriate antidiuresis were taken into account. The aim of the study was to discuss the differential diagnosis of chronic euvolemic hyponatraemia and to draw attention to the need for genetic testing for the nephrogenic syndrome of inappropriate antidiuretic hormone secretion caused by activating point mutations of the vasopressin 2 receptor gene (*V2R*).

Keywords: hyponatraemia, nephrogenic syndrome of inappropriate antidiuresis (NSIAD), syndrome of inappropriate antidiuretic hormone secretion (SIADH), cerebral salt wasting syndrome (CSWS), children

Streszczenie

Prawidłowe stężenie sodu w płynie pozakomórkowym wynosi 135–145 mmol/l. Niskie stężenie sodu w surowicy (hiponatremia) jest jednym z częstych zaburzeń gospodarki wodno-elektrolitowej. U dzieci najczęstszą przyczyną hiponatremii jest odwodnienie lub przewodnienie. W niniejszej pracy opisano przypadek 2,5-letniego chłopca, który został przyjęty na oddział pediatryczny z powodu zapalenia płuc. U dziecka stwierdzono niechęć do przyjmowania płynów, hiponatremię hipoosmolalną z hipourykemią, zwiększone wydalanie sodu z moczem, bez zaburzeń w stanie nawodnienia. W wywiadzie rodzinnym odnotowano utrzymującą się hiponatremię i nadciśnienie tętnicze u dziadka chłopca. W diagnostyce różnicowej, po wykluczeniu chorób przysadki mózgowej, tarczycy, kory nadnerczy, zaburzeń funkcji nerek, procesów rozrostowych, pod uwagę brano zespół utraty soli pochodzenia mózgowego, zespół nieadekwatnego wydzielania wazopresyny oraz nerkopochodny zespół nieadekwatnej antydiurezy. Cele pracy obejmują przedstawienie diagnostyki różnicowej przewlekłej hiponatremii euwolemicznej oraz zwrócenie uwagi na potrzebę wykonywania badań genetycznych w kierunku nerkopochodnego zespołu nieadekwatnego wydzielania wazopresyny, spowodowanego aktywującymi mutacjami punktowymi genu receptora wazopresyny 2 (*V2R*).

Słowa kluczowe: hiponatremia, nerkopochodny zespół nieadekwatnej antydiurezy (NSIAD), zespół nieadekwatnego wydzielania wazopresyny (SIADH), zespół utraty soli pochodzenia mózgowego (CSWS), dzieci

INTRODUCTION

Normal sodium levels in extracellular fluid are in the range of 135–145 mmol/L. Only 7% fluctuations are tolerable[1]. As the main extracellular cation, sodium determines plasma osmolality, maintaining proper volume of the extracellular space. In clinical practice, abnormal regulation of extracellular water (dehydration or hyperhydration) and, less often, sodium excess or deficiency, are the most common cause of impaired natraemia in children[2]. Low serum sodium (hyponatraemia) is a common disorder of water and electrolyte balance.

The classification of hyponatraemia[3] is based on the following criteria:

1. serum sodium levels:
   - mild hyponatraemia – 130–134 mmol/L,
   - moderate hyponatraemia – 125–129 mmol/L,
   - severe hyponatraemia – <125 mmol/L;
2. progression rate:
   - acute hyponatraemia, with documented duration of <48 hours,
   - chronic hyponatraemia, lasting >48 hours and where it is not possible to determine its duration;
3. the presence of clinical symptoms:
   - symptomatic hyponatraemia,
   - asymptomatic hyponatraemia;
4. plasma osmolality:
   - hypotonic hyponatraemia,
   - isotonic hyponatraemia,
   - hypertonic hyponatraemia;
5. child's hydration status:
   - hyponatraemia with hypovolaemia,
   - hyponatraemia with euvolemia,
   - hyponatraemia with hypervolemia.

Hyponatraemia may be responsible for a wide range of symptoms, mainly from the central nervous system (CNS), ranging from mild to severe and even life-threatening. The spectrum of symptoms includes, among others, nausea, vomiting, bradyphrenia, distraction, headache, somnolence, convulsions, coma and even status epilepticus. Cerebral oedema, which most often develops when sodium levels are corrected too quickly, may be a dangerous complication of acute hyponatraemia.

The variety of disorders accompanied by hyponatraemia may contribute to diagnostic and therapeutic challenges. In 2014, the European Renal Best Practice (ERBP)[3] guidelines for the diagnosis and treatment of hyponatraemia, developed jointly by three scientific societies: European Society of Intensive Care Medicine (ESICM), European Society of Endocrinology (ESE) and the European Renal Association – European Dialysis and Transplant Association (ERA/EDTA) were published; the Polish version of these guidelines was published in 2015[4]. We present this case report to discuss the aetiological differentiation of chronic normovolemic hyponatraemia.

CASE REPORT

A 2.5-year-old boy was admitted to the paediatric unit. He had a medical history of 3-day fever of up to 40°C, which was followed by respiratory symptoms with mild dyspnoea. Physical examination revealed auscultatory changes over the lung fields: rales, crackles, tachypnoea, involvement of additional respiratory muscles (diaphragmatic and intercostal retractions), and tooth decay. No oedema or other signs of hyperhydration or dehydration were observed. He had blood pressure of 99/59 mm Hg, heart rate of 79 bpm, and diuresis of 300 mL. Physical development parameters: height 93 cm (25^{th} percentile), body weight 12 kg (3^{rd} percentile), body mass index (BMI) of 14.2 kg/m^2 (10^{th} percentile).

The boy was born from first pregnancy, first delivery (vaginal), full term, with a birth weight of 2,848 g and an Apgar score of 10. The child's psychomotor development has been normal so far, without a medical history of neurological symptoms, also in the case of febrile infections. The boy was observed to reluctantly consume water, had a very low intake of fluids (about 500 mL/day), but willingly consumed milk-based meals.

His family history revealed long-term hyponatraemia of 123–130 mmol/L with hypertension in his 62-year-old maternal grandfather; other immediate family members were healthy, without ion disorders in laboratory tests.

Laboratory tests on admission to the district hospital showed that the boy had high inflammatory markers: C-reactive protein (CRP) 44.5 mg/dL, white blood cell count (WBC) 19.7 thousand/μL and hyponatraemia 125 mmol/L (Tab. 1). Serum potassium, creatinine and urea levels were normal. Red blood cells (5–10 in the field of vision) and ketones (+) were present in urine; transient glucosuria was also found (473 mg/dL), with serum glucose of 98–76 mg/dL. Chest X-ray showed severe peribronchial changes, while abdominal ultrasound showed small hyperechoic reflections in the walls of the pelvicalyceal system, without any signs of typical ultrasound deposits, which were not confirmed in further tests.

Antibiotic therapy (intravenous cefuroxime), antipyretic treatment and intravenous hydration with 0.9% NaCl were used.

Follow-up laboratory tests performed after hydration showed persistent hyponatraemia (132 mmol/L), with normal potassium, calcium, magnesium, phosphorus, and chlorine ions. Low uric acid (1 mg/dL) was noticeable. Serum osmolality remained at the lower limit of normal (295 mOsm/kg H_2O); urine osmolality was 756 mOsm/kg H_2O. The boy was transferred to the nephrology department.

Subsequent laboratory tests performed in a good health condition of the child revealed hyponatraemia (125–132 mmol/L), a tendency to hypochloraemia (91–96 mmol/L), and low uric acid (1.1 mg/dL). Serum osmolality was reduced (275–260 mOsm/kg H_2O), urine osmolality was normal (872–860 mOsm/kg H_2O). Sodium level in the urine sample was high, ranging from 86 to 194 mmol/L.

Serum thyroid hormones, adrenocorticotropic hormone, cortisol, renin and aldosterone were within normal limits,

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Serum/plasma	Day 1	Day 5 (after hydration)	Day 12	Day 42	1 year later	13 months later	Reference
Sodium [mmol/L]	125	132	125	132	120	127	132–145
Potassium [mmol/L]	3.9	4.6	4.6	5.1	4.5	4.6	3.5–5.1
Phosphorus [mg/dL]	–	4.9	5.8	5.4	4.8	5,1	3.9–6.5
Total calcium [mg/dL]	–	9.8	9.9	10.6	9.9	10.3	8.7–10.8
Magnesium [mg/dL]	–	2.1	2.1	2.2	2	2.3	1.5–2.4
Chlorine [mmol/L]	–	98	91–96	100	–	91	96–108
Creatinine [mg/dL]	0.47	–	0.20	0.20	0.20	0.28	0.20–0.47
Urea [mg/dL]	19.7	–	28	28	14.4	13.5	10.7–36.4
Uric acid [mg/dL]	–	1	1.1	2.1	1.2	1.6	1.8–5.0
Serum osmolality [mOsm/kg H_2O]	–	295	275	–	260	–	275–295
Urine – a random sample							
Urine osmolality [mOsm/kg H_2O]	–	756	872	–	628	–	275–900
Specific gravity	1.016	1.021	1.025	1.025	1.020	1.025	1.002–1.035
Na [mmol/L]	–	194	86	119	148	124	≤30 mmol/L*
Fractional excretion of sodium FE_{Na}	–	–	0.30%	0.60%	0.54%	0.54%	<0.5%**
Fractional excretion of urinary acid FE_{UA}	–	–	30%	17.6%	–	21%	<12%

Blue background – decreased biochemical parameters.
Pink background – elevated biochemical parameters.
* No reference values for urine sodium (depending on the diet and clinical circumstances of the patient) (see[5]).
** Values dependent on glomerular filtration rate and sodium intake (see[6]).

Tab. 1. Patient's blood and urinary findings

whereas serum copeptin (preprovasopressin) was found to be very low (<2.7 pmol/mL) (Tab. 2).

Due to the family history of hyponatraemia with arterial hypertension in the boy's grandfather, genetic tests for type I pseudohypoaldosteronism were conducted. Next generation sequencing (NGS) of *CUL3*, *HSD11B2*, *KLHL3*, *NR3C2*, *SCNN1A*, *SCNN1B*, *SCNN1G*, *WNK1*, *WNK4* revealed no pathogenic or potentially pathogenic variants for type I pseudohypoaldosteronism. Magnetic resonance imaging of the brain was performed and was normal. Due to the low serum copeptin, genetic tests for activating mutation of the type 2 vasopressin receptor gene were performed, the results of which are still awaited (the material was sent to a foreign centre).

The treatment involved limited fluid intake and adding salt to meals.

DISCUSSION

In the presented case of chronic hyponatraemia, the principles of multi-stage diagnosis of hyponatraemia were followed.

1. Stage I – determining actual serum sodium

Plasma glucose should be measured in all cases and if >100 mg/dL, the measured sodium should be corrected using one of the following formulas[3,4]:

- **corrected sodium** = measured sodium [Na^+] + 2.4 × [glucose level [mg/dL] – 100 [mg/dL]] : 100 [mg/dL] or
- **corrected sodium** = measured sodium [Na^+] + 2.4 × [glucose level [mmol/L] – 5.5 [mmol/L]] : 5.5 [mmol/L].

This should be followed by differentiation between true and pseudohyponatraemia based on plasma osmolality:

- 275–295 mOsm/kg H_2O – pseudohyponatraemia;
- >295 mOsm/kg H_2O – non-hypotonic hyponatraemia;
- <275 mOsm/kg H_2O – hypotonic (true) hyponatraemia.

Pseudohyponatraemia is characterised by normal plasma osmolality and may develop as a result of hyperlipidaemia or hyperproteinaemia. Sodium measurement using sodium ion selective electrodes is error-free and reliable[2].

Non-hypotonic, hyperosmolar hyponatraemia may occur with hyperglycaemia or after mannitol administration. An increase in plasma osmolality due to high levels of glucose or other osmotically active substances causes a shift of water into the extracellular space, which decreases sodium levels.

True hyponatraemia is always associated with decreased plasma osmolality and is hypotonic.

Hormone	Copeptin*	Lying aldosterone	Standing aldosterone	Lying renin	Standing renin	ACTH	Cortisol	TSH	fT4
Reference	0.81–28.2 pmol/mL	1.76–23.2 ng/dL	2.52–39.2 ng/dL	2.8–39.9 µIU/mL	4.4–46.1 µIU/mL	7–67.3 pg/mL	1.7–14.4 µg/dL	0.66–4.65 µIU/mL	0.89–1.72 µIU/mL
Result	<2.7	14.7	9.64	13.7	9	20.9	6.6	1.31	1.07

ACTH – adrenocorticotropic hormone; **fT4** – free thyroxine; **TSH** – thyroid-stimulating hormone.
* Preprovasopressin; reference values depend on blood osmolality.

Tab. 2. Hormonal findings in the patient

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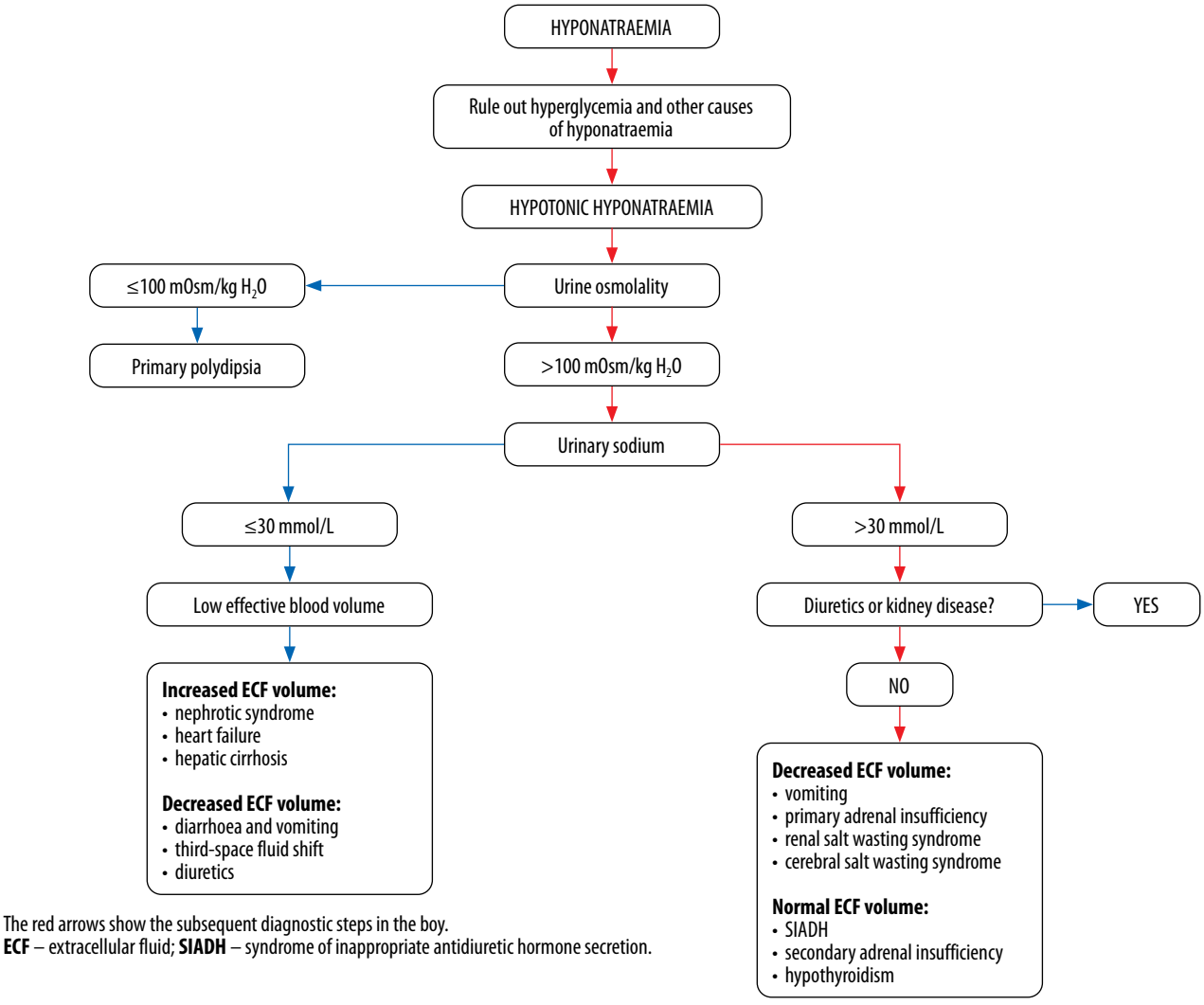

The red arrows show the subsequent diagnostic steps in the boy.
ECF – extracellular fluid; **SIADH** – syndrome of inappropriate antidiuretic hormone secretion.

Fig. 1. Diagnostic algorithm for hyponatraemia (author's modification according to[3])

The described patient had normal blood glucose, sodium ranging from 120 to 132 mmol/L, no lipid disorders, and normal proteinogram, which excluded pseudohyponatraemia. Borderline plasma osmolality was observed – 275 mOsm/kg H_2O, and even 260 mOsm/kg H_2O in subsequent tests; therefore, hyponatraemia was classified as hypotonic (true).

2. **Stage II – an assessment of the patient's hydration status to diagnose hyponatraemia:**

- hypovolemic with true sodium deficiency;
- normovolemic (euvolemic);
- hypervolemic (water intoxication; dilutional hyponatraemia).

Since our patient showed no signs of overhydration or dehydration, only the causes of hypotonic, normovolemic/euvolemic hyponatraemia were considered in further differentiation.

3. **Stage III – search for the causes of hypotonic and normovolemic hyponatraemia**

At this stage, urine osmolality and the amount of sodium excreted in a random urine sample should be determined, the collection of which should be timed with blood sampling, so that the interpretation of the obtained findings is correct (Fig. 1).

The patient had urine osmolality of >100 mOsm/kg H_2O and sodium excretion of >30 mmol/L. Kidney function was normal. It should be noted that kidney diseases make the differential diagnosis of hyponatraemia very difficult, as urine osmolality and sodium excretion may be disturbed and fail to reflect normal relationships in water and sodium balance.

The differential analysis of the causes of hypoosmolar, hypotonic and normovolemic hyponatraemia in the described patient included endocrine disorders, salt-wasting syndromes and syndromes of inappropriate antidiuretic hormone secretion.

Thyroid hormones, ACTH, cortisol, renin and aldosterone remained within the normal range, which allowed to exclude hypothyroidism, pituitary, primary/secondary adrenal insufficiency. Genetic testing ruled out type I pseudohypoaldosteronism. Brain imaging was normal. Low copeptin was noticeable.

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Parameters	CSWS	SIADH	NSIAD
Serum sodium	↓	↓	↓
Urine sodium	↑	↑	↑
Serum osmolality	↓ or =	↓	↓
Urine osmolality	↑ or =	↑	↑ or =
Urine volume	↑	↓ or =	↓
Serum antidiuretic hormone	↑	↑	↓ / undetectable
Hydration status	↓ or =	↔	↔

CSWS – cerebral salt wasting syndrome; **SIADH** – syndrome of inappropriate antidiuretic hormone secretion; **NSIAD** – nephrogenic syndrome of inappropriate antidiuresis.

Tab. 3. Typical features of CSWS, SIADH, NSIAD

Copeptin (CT-proAVP) is a 39-amino acid polypeptide, which is the C-terminal fragment of provasopressin. It is currently considered a clinically useful surrogate marker for arginine vasopressin (AVP) as, unlike AVP, it has a long half-life and does not bind to platelets[7,8]. It is found in plasma at a higher level than AVP, and its value closely correlates with plasma AVP.

Further diagnosis considered the possibility of cerebral salt wasting syndrome (CSWS), nephrogenic syndrome of inappropriate antidiuresis (NSIAD) and syndrome of inappropriate antidiuretic hormone secretion (SIADH) (Tab. 3)[4,9,10].

- **CSWS**

This disorder develops in patients with CNS damage, most often after neurosurgical procedures, as a result of subarachnoid bleeding; in the course of meningitis, tuberculosis meningitis in particular, and neoplastic processes.

The pathomechanism of CSWS has still not been fully explained; however, increased sodium loss in the urine, leading to polyuria and reduced intravascular volume, which stimulates baroreceptors and increases the secretion of natriuretic peptides, is its characteristic feature.

Hyponatraemia in CSWS is secondary to natriuresis rather than increased water retention. The observed increase in AVP may cause the transition of the hypovolemic phase of the disorder into the euvolemic phase; therefore, CSWS was considered in the differential diagnosis in the described case.

The diagnosis of CSWS is based on decreased plasma osmolality with concomitant urinary hyperosmolarity and increased excretion of sodium in the urine[10]. Polyuria, which was not present in our patient, is typically seen in CSWS. On the contrary, the boy reluctantly consumed fluids and passed small amounts of urine.

- **SIADH**

Excessive secretion of antidiuretic hormone in relation to plasma osmolality is the essence of this disorder. As a result, the amount of urine excreted is reduced by its excessive concentration, which in turn leads to dilution hyponatraemia and euvolemia with accompanying plasma hypoosmolality. Additionally, urinary hyperosmolarity, increased excretion of sodium in the urine, and increased fractional excretion of uric acid are present (FE_{UA} >12%) (Tab. 4). Laboratory work-up shows normal parameters of kidney, adrenal and thyroid function.

Cancer, injuries, CNS pathology, pneumonia, and certain medications lead to the development of SIADH. Fluid restrictions combined with salt intake are used in the treatment of SIADH. Once hyponatraemia is corrected, additional furosemide may be used. Vaptans (tolvaptan, conivaptan), which may be used in adults, are not approved for children.

Although the boy met the diagnostic criteria for SIADH, one of its subtypes (NSIAD) was contemplated due to his family history of hyponatraemia.

- **NSIAD**

NSIAD is a rare disorder caused by a point mutation of the vasopressin receptor (*V2R*) gene located on the X chromosome, most often at R137C and R137L, but also at F229V, I130N, L312S[12], resulting in constitutive activation of type-2 vasopressin receptor (*V2R*)(C). The disorder manifests with hyponatraemia, euvolemia, plasma hypoosmolality with concomitant urinary hyperosmolality, increased natriuresis and increased fractional excretion of uric acid (FE_{UA}).

The clinical picture is similar to that of SIADH; therefore, NSIAD is considered one of its subtypes. Low or undetectable AVP in NSIAD, which in turn is high in SIADH, is a feature differentiating both diseases. Fluid restriction and sodium normalisation may increase AVP, because then its secretion is not inhibited.

Although NSIAD usually manifests in early infancy, the diagnosis may not be reached until adulthood. Adult patients are usually asymptomatic or develop only mild symptoms[13]. Water stress test may be useful for diagnostic purposes in elderly and asymptomatic patients. Patients with NSIAD are not able to remove excess water from the body, which further aggravates hyponatraemia. However, the test is not recommended for neonates and infants.

AVPR2 sequencing is performed to confirm the diagnosis. About 30 cases of NSIAD have been described worldwide since the first diagnosed case of the syndrome in 2005[14–17]. A familial/genetic predisposition to NSIAD is possible, but sporadic cases may be also observed.

The therapy is primarily based on fluid restriction, which is most controversial in the case of newborns and small infants due to the limited possibilities of reducing the intake of breast milk or formulas while maintaining an adequate daily caloric requirement.

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Primary criteria for syndrome of inappropriate antidiuretic hormone secretion
✓ **Effective serum osmolality <275 mOsm/kg H_2O**
✓ **Urine osmolality >100 mOsm/kg H_2O with reduced effective osmolality**
✓ **Euvolemia (in clinical evaluation)**
✓ **Urine sodium >30 mmol/L with normal dietary sodium and water intake**
✓ **No adrenal, thyroid, pituitary or renal failure**
✓ **No use of thiazide diuretics**
Supplementary criteria
✓ **Serum uric acid<0.24 mmol/l (<4 mg/dL)**
✓ **Serum urea <3.6 mmol/L (<21.6 mg/dL)**
✓ Failure to correct hyponatraemia with intravenous infusions (0.9% NaCl)
✓ **Fractional excretion of sodium – FE_{Na} >0.5%**
✓ Fractional excretion of urea – FE_{urea} >55%
✓ **Fractional excretion of uric acid – FE_{UA} >12%**
✓ Correction of hyponatraemia by limiting oral fluid intake
Criteria met by the patient are given in bold.

Tab. 4. Diagnostic criteria for the syndrome of inappropriate antidiuretic hormone secretion, taking into account the patient's laboratory findings (author's modification according to[11])

In the case of NSIAD, oral preparations of urea, which stimulate osmotic diuresis, proved to be effective both in adults and children[18]. Urea preparations reduce natriuresis by maintaining water removal. They may be particularly useful in children in whom severe fluid restriction may be dangerous or difficult to achieve. They are effective, safe and inexpensive. Additionally, they may be used over a long time. Difficulties in diagnosing chronic hyponatraemia in the presented case resulted from the fact that, despite meeting the criteria for SIADH, the cause of this syndrome could not be clearly determined due to normal brain magnetic resonance imaging, lack of injuries or a history of CNS diseases.

On admission, the boy presented with signs of pneumonia, which theoretically may result in SIADH, but this is usually seen in severe pneumonia with complications. Furthermore, SIADH is a transient condition, whereas chronic hyponatraemia was observed in the described patient.

No polyuria was found in the patient, which ruled out CSWS.

The history of the child's reluctance to drink water and poor urine excretion were more typical of NSIAD than SIADH. Low copeptin (preprovasopressin) was indicative of NSIAD. The final diagnosis of NSIAD in this case may be confirmed by a genetic test for an activating mutation of the vasopressin receptor (*V2R*) gene located on the X chromosome, the results of which are still awaited.

CONCLUSIONS

Correct determination of the aetiology of euvolemic hyponatraemia may pose challenge, especially in its chronic form, which may be determined genetically.

A thorough family history may be helpful in finding the cause of hyponatraemia.

NSIAD is a very rare disorder; however, it should be considered in a situation where the patient meets the criteria for hypotonic hyponatraemia, euvolemic hyponatraemia and SIADH syndrome, the cause of which cannot be explained. Undetectable or very low levels of vasopressin are the hallmark of NSIAD. Genetic testing to search for mutations associated with NSIAD should be performed to confirm the diagnosis.

Conflict of interest

The authors do not declare any financial or personal links to other persons or organisations that could adversely affect the content of this publication or claim rights thereto.

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