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Case Report

Nephrogenic syndrome of inappropriate antidiuresis – a case report in pediatric age

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Abstract

Syndrome of inappropriate antidiuresis (SIAD) results in hyponatremia, low plasma osmolality, euvolemia and inappropriately concentrated urine with high sodium excretion. In most cases, there is an inappropriate secretion of arginine vasopressin (AVP); however, in a minority of cases, there is a gain-of-function mutation in the AVP receptor 2 -nephrogenic SIAD. We pretend to describe an interesting nephrogenic SIAD case caused by a pathogenic variant c.409C>T p.(Arg137Cys) in hemizygosity in the AVPR2 gene.

Keywords: Nephrogenic syndrome; Hyponatremia; Antidiuretic hormone

Introduction

Water balance depends on the intact thirst mechanism, which is mediated by the hypothalamus, and on the regulation of kidney water loss, mediated by arginine vasopressin (AVP), sometimes referred to as antidiuretic hormone [1]. Disorders in water balance may compromise homeostasis [1]. Diabetes insipidus (DI) is the result of a deficiency of AVP caused by a lesion in the hypothalamus (central DI) or by an inactivating mutation in the AVP receptor 2 (AVPR2) in the renal collecting duct (nephrogenic DI). Usually, the clinical manifestations include polyuria, polydipsia and hypernatremia. In opposition, the syndrome of inappropriate antidiuresis (SIAD) results in hyponatremia (<135 mmol/L), low plasma osmolality (<275 mOsm/kg), euvolemia and inappropriately concentrated urine (>100 mmOsm/kg) with high sodium excretion (> 40 mmol/L [2-6]. It is considered to be a diagnosis of exclusion, once it requires euvolemia without renal, thyroid or adrenal insufficiency or recent use of diuretic drug [1,2,5,6]. Causes of SIAD include malignancy, pulmonary or neurologic disorders, some drugs, pain and nausea, among others [2,5]. In most cases there is an inappropriate secretion of AVP, however in 10-20% of patients AVP release is suppressed – SIAD type D, in which the inappropriate antidiuresis is independent of AVP [2,7], due to secretion of an unidentified antidiuretic substance from tumor cells or due to nephrogenic SIAD (NSIAD) [6]. NSIAD is caused by gain-of-function mutations in the gene encoding AVPR2 on chromosome Xq28 [2,6]. Until 2023, a total of 59 cases of NSIAD from 23 families were reported by Tong HF et al, Mammadova J et al. and Gavryutina I et al, 20 of which were diagnosed in pediatric age [2,4,8]. We pretend to describe an interesting case of nephrogenic SIAD.

Case report

A boy, the son of non-consanguineous parents, followed in a neurodevelopment consultation since he was five months old due to delayed psychomotor development, axial hypotonia and minor dysmorphisms. At two years of age, an analytical evaluation was performed. It revealed hyponatremia of 122 mEq/L (reference value 135-145 mEq/L), as well as low plasma osmolarity (250 mOsm/kg) and increased urinary osmolarity (1240 mOsmol/kg) with high sodium excretion (59 mEq/L). He had a normal concentration of potassium and bicarbonate and was clinically euvolemic, with normal blood pressure and heart rate. At this time, the AVP level was not measured. There was no history of polydipsia, chronic diarrhoea, or usual drug therapy, including diuretics. Family history was irrelevant. Renal, thyroid and adrenal function were normal. He also performed a brain magnetic resonance and a chest radiography that showed no significant alterations. The kidney ultrasound was also normal. At that time, he started 20% sodium chloride supplementation (4,5 mEq/kg/day of sodium, four times a day) and fluid restriction, with an improvement in neurodevelopment (especially in locomotor and speech and hearing areas). The AVP level was measured after the initiation of sodium supplementation and fluid restriction, and was normal (4,8 pg/mL) at that point. The genetic study was performed and revealed a pathogenic variant c.409C>T p.(Arg137Cys) in hemizygosity in the AVPR2 gene, which confirms the diagnosis of nephrogenic syndrome of inappropriate antidiuresis.

Discussion

Nephrogenic syndrome of inappropriate antidiuresis (NSAID, ORPHA:93606) is a very rare X-linked disease presenting with hyponatremia, hyposmolarity, euvolemia, inappropriately concentrated urine, increased natriuresis, and undetectable or very low AVP circulating levels [2,3,6]. It can occur in neonates, children or even later in life [2,3]. NSIAD must be recognized and treated early to prevent severe hyponatremia, which can lead to death or neurologic sequelae [3,4]. The most common onset in neonates and infants is characterized by acute hyponatremia accompanied by seizures and/or

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irritability [3,7]. In contrast, late-onset cases often show a wide spectrum of symptoms and severity levels [3]. The degree of hyponatraemia may not correlate with the severity of symptoms [2]. As an X-linked disorder, female carriers are usually asymptomatic but may have mild hyponatraemia [2].

In many of the described cases, low or undetectable AVP levels are reported during severe hyponatremia, usually coinciding with the clinical onset or time of diagnosis [3]. However, with the treatment, AVP levels can rise and reach the normal range [3]. The mainstay of treatment is fluid restriction [1,3,4], but NaCl supplementation and/or urea administration may also be needed [3]. In addition, tolvaptan, a selective oral AVPR2 antagonist, may be used for specific pathogenic variants (F229V, I130N and L312S) in AVPR2 [2]. Our patient had normal AVP levels after starting fluid restriction and NaCl supplementation, with no previous dosing and had a neurodevelopment delay and axial hypotonia that improved after treatment, which has already been described by Gavryutina I,et al [8].

Confirming the diagnosis of NSIAD by sequencing the AVPR2 gene is important to end the diagnostic odyssey, enhance patients' and their parents' management, and allow the possibility of genotype-guided personalized therapy with vaptans and genetic counselling [2].

The long-term outcome of patients affected by NSIAD is generally good [7] if sodium levels are well controlled.

Conclusion

NSIAD should be suspected in cases of hyponatremia and high urinary osmolality, increased natriuresis and low plasma osmolality. AVP levels should be measured during hyponatremic episodes and low or undetectable levels suggest the diagnosis of NSIAD. NSIAD must be recognized and treated early to prevent severe hyponatremia, which can lead to death or neurologic sequelae in case of survival. Diagnosis can be confirmed by sequencing the AVPR2 gene.

Conflict of interest

The authors declare that there were no financial disclosures nor conflicts of interest in conducting this work.

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