

Asymptomatic Hyponatremia Revealing Inappropriate Secretion of ADH Syndrome In a Patient with Triple A Syndrome

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Abstract

Context: Allgrove's syndrome or triple A syndrome (AAA), combines Addison's disease with alacrimia and achalasia. In this context, hyponatremia would suggest acute adrenal insufficiency and initiate replacement therapy. However, other etiologies are possible including SIADH. To the best of our knowledge, this combination of Syndrome 3A and SIADH has not been reported.

Objectives: Describe the etiological and therapeutic particularities of a rare association between AAA syndrome and SIADH.

Materiel and Methods: We present the case of a patient followed for AAA syndrome and depression, in whom a profound hyponatremia discovered incidentally related to idiopathic SIADH.

Design: a case report of a patient hospitalized in endocrinology department in 2018

Observation: This is a report of a patient whose AAA syndrome was genetically confirmed at the age of 4 years. At 25, she was hospitalized for investigation of asymptomatic hyponatremia at 119 mmol/L. She was receiving 20 mg of hydrocortisone and 100 mcg of fludrocortisone. Olanzapine, added 3 years ago due to behavioral disorders, had already been stopped by the patient for months. The diagnosis of acute adrenal crisis was ruled out. Plasma osmolality was 243 mosm/L, with inadequate natriuresis at 118 mmol/24 h. The SIADH diagnosis was retained. Natremia was corrected after fluid restriction. The etiological investigation of this SIADH was negative.

Conclusion: The association of SIADH with syndrome 3A requires patient education in order to maintain a satisfactory state of fluid and electrolyte balance. Olanzapine, should not probably be reintroduced in this patient.

Keywords: Allgrove's Syndrome; Allgrove's Syndrome or Triple A Syndrome (AAA)

Introduction

Allgrove's syndrome or triple A (AAA) is a rare recessive autosomal disease associating Addison's disease, alacrimia and achalasia. Since adrenal insufficiency is a feature of AAA syndrome, hyponatremia is usually an indicator of acute adrenal crisis. However, other etiologies including SIADH should be evoked. Differentiating hyponatremia related to adrenal crisis from SIADH is essential, since misdiagnosis can be life-threatening. The association of Allgrove's syndrome and SIADH related hyponatremia has not been reported to our knowledge. We report a case of a patient with AAA

syndrome presenting with an asymptomatic profound hyponatremia due to SIADH.

Case Report

A 25 years old patient was received at her usual consultation appointment, the routine laboratory work-up showed low isolated levels of plasma Sodium at 119 mmol per liter.

She had consanguineous parents and her four-and-half years old sister died several years ago in a context of acute adrenal crisis.

The patient was diagnosed with Addison’s disease at the age of four years and have received Hydrocortisone and Fludrocortisone. Initial presentation included vomiting, loss of weight and appetite and intense hyperpigmentation.

Parents reported congenital alacrimia, which evoked for pediatricians the “Allgrove’s syndrome”. Genetic testing for mutation of the AAAS gene confirmed the diagnosis.

Up to 25 years of age, our patient presented no episodes of acute adrenal crisis. An esophageal manometry was performed twice and hadn’t shown achalasia. A growth delay was noticed within years. And the patient suffered from behavioral abnormalities and hallucinations for which she referred 3 years prior to her admission to the outpatient psychiatry consultation. An Olanzapine prescription improved her condition.

At her last usual consultation, low levels of plasma Sodium at 119 mmol per liter were noticed. Levels of Potassium and Chloride in the blood were within normal ranges. At that time, the treatment of our patient included 20 mg of Hydrocortisone and 100µg of Fludrocortisone daily.

She claimed taking her medication regularly. She was doing well and had no hypoglycemia.

Even there was no clinical sign or other biological feature suggestive of adrenal crisis, the patient was admitted into the endocrinology department for further investigation.

At admission, she was afebrile and hemodynamically stable and without any signs of active infectious disease. There was no edema. Thyroid palpation was normal.

Neurological evaluation revealed a quadripyramidal spasticity and acerebellar ataxia.

On the laboratory tests (Table 1), the liver and kidney functions were normal. Her Thyroid –Stimulating Hormone level was also normal.

Plasma osmolality was however decreased at 243 mosmol /l.

Urinary Sodium and osmolality were both elevated at 76 mmol/l and 378 mosmol /l respectively.

Table1: Biochemical work-up at initial presentation

Exam	Result	Reference Value
Plasma Sodium (mmol/l)	118	135-145
Plasma Potassium (mmol/l)	3.75	3.5-5
Urinary Sodium (mmol/l)	35	< 20
Urinary Potassium (mmol/l)	23	< 10
Plasma osmolality (mosmol/L)	243	285
Urinary osmolality(mosmol/L)	378	100-300
Thyroid-Stimulating Hormone(mUI/L)	0.85	0.25-4
Plasma Calcium (mmol/l)	2.3	2.25-2.65
Creatinine (µmol/l)	38	50-120
Urea (mmol)	2.6	2.5-7.5

Decreased effective osmolality of the extracellular fluid (Posm 100 mOsmol/kg H₂O)

Inappropriate urinary concentration (Uosm>100 mOsmol/kg H₂O) with normal renal function) at some level of plasma hypo-osmolality.

Clinical euvoolemia, as defined by the absence of signs of hypovolemia (orthostasis, tachycardia, decreased skin turgor, dry mucous membranes) or hypervolemia (subcutaneous edema, ascites).

Elevated urinary sodium excretion (>20-30 mmol/L) while on normal salt and water intake.

Absence of other potential causes of euvolemic hypo-osmolality: severe hypothyroidism, hypocortisolism (glucocorticoid insufficiency).

Normal renal function and absence of diuretic use, particularly thiazide diuretics.

Box 1: Diagnosis criteria for SIADH (adapted from [8]).

At this point, since all other causes of hyponatremia were excluded, inappropriate secretion of Anti-Diuretic Hormone Syndrome (SIADH) was retained.

Etiological diagnosis of this secretion was then carried-on.

Olanzapine-related SIADH was suspected. The patient denied, however, any use of this treatment for the last few months and the hyponatremia wasn't improving despite hospitalization, medications were offered by nurses.

There was no clinical nor biological evidence of infectious, inflammatory or tumoral diseases and thoraco-abdominal Tomodensitometry showed no abnormalities except bilateral adrenal atrophy related to her Addison's disease.

The patient was put on fluid restriction (500 ml per day), and plasma sodium levels were normal again after 6 days. The patient was discharged and ulterior follow-up showed persistent normal levels of plasma sodium.

Discussion

We report here a unique case of a 25 years old woman having an Allgrove's syndrome, presenting with asymptomatic severe hyponatremia, while she was adequately treated since the age of four with hydrocortisone and fludrocortisone for her primary adrenal insufficiency (PAI). This hyponatremia was connected to an idiopathic SIADH.

This would be (to our knowledge) the first described association of these two conditions.

PAI is indeed an uncommon but potentially lethal condition [1,2]. The early death of the sister of our patient was probably to an acute adrenal failure since PAI wasn't suspected earlier.

PAI is characterized by a deficiency of glucocorticoids, with an inconstant deficiency in mineralocorticoids and androgens. In adults, the most frequent causes are the auto-immunedestruction of the adrenal glands and tuberculosis [3]. But among children, congenital adrenal hyperplasia (CAH) in its classic form of 21 hydroxylase deficiency is the most frequent cause [2,3].

Our patient was first tested for this deficiency, but CAH was quickly ruled out.

Other causes of PAI among children are mainly represented by genetic diseases. Among which, the adrenoleukodystrophy remains the most frequent [3,4], followed by Allgrove's syndrome or triple A (AAA) syndrome [5,6].

Triple-A syndrome is a rare autosomic recessive disease, characterized by an adrenocorticotrophic hormone (ACTH) resistant adrenal insufficiency, alacrimia and achalasia of the esophageal cardia. Genetically it is due to the mutation of AAAS gene, located on chromosome 12q13, encoding to a nuclear envelope protein known as ALADIN (alacrimia-achalasia-adrenal insufficiency neurologic) protein [5-7].

For our patient with PAI, since CAH was ruled out, after parents reported alacrimia, the diagnosis of AAA syndrome was made very probable. Genetic testing for mutation of the AAAS gene confirmed the diagnosis at the age of four.

Esophageal manometry was performed twice and didn't show achalasia. In a Tunisian study including 26 patients diagnosed with AAA syndrome, 100% presented Addison's disease and alacrimia, while 88% had achalasia and only 27% presented with neurologic abnormalities [6].

Neurological evaluation for our patient revealed a quadripyramidal spasticity and a cerebellar ataxia.

Other clinic features of Allgrove's syndrome include progressive central, peripheral or autonomous neurological impairment with or without mental retardation [5,6], hyperkeratosis, developmental delays, and microcephaly [6]. Our patient suffered from growth delay and behavioral abnormalities.

AAA syndrome is rare but hyponatremia is one of the most frequent abnormalities of electrolyte homeostasis [8].

It is frequently associated with adverse outcomes, especially in the context of frail patients or acute hyponatremia.

Our patient had no suggestive symptoms of acute hyponatremia, which usually manifests with neurological symptoms, such as seizures, dyskinesia, psychosis or coma [9].

Diagnosis of the cause of Hyponatremia is an essential step for the treatment, and is mainly based on the assessment of extracellular fluid volume and plasma osmolarity [8].

In our case, we firstly suspected acute adrenal crisis since the patient had PAI and was treated with hydrocortisone and fludrocortisone. But she claimed being compliant with the treatment, didn't suffered from acute adrenal failure during her follow-up and did not reported abdominal pain or vomiting.

Physical examination didn't showed signs of dehydration, the laboratory work-up didn't show hypoglycemia or hyperkalemia. The acute adrenal failure was less likely.

Since the patient presented no signs of dehydration or edema, we were facing an euvolemic hyponatremia whose main cause is SIADH. Other causes include isolated glucocorticoids deficiency and hypothyroidism [8]. TSH level was within the normal ranges. Diagnosis criteria for SIADH were fulfilled for our patient (Box1).

In our case, misdiagnosing the cause of hyponatremia could have been weighty. Since symptomatic treatments of the acute adrenal crisis consist of intravenous isotonic fluids and injections of hydrocortisone, the fluid expansion in our case could have worsened the hyponatremia.

SIADH is due indeed to an increased anti diuretic action of ADH and tubular reabsorption of water. The slight increase of extracellular water leads to hyponatremia, and the elevation of plasma natriuretic peptide explains the absence of edema [10].

On another hand, treating a patient as having SIADH while suffering from an acute adrenal failure could be lethal since fluid restriction could lead him to potential collapses and dehydration [11,12].

Our patient responded well to fluid restriction and her sodium levels were normal in just few days and persisted normal after being discharged.

Investigation the underlying cause for SIADH is also an important step since hyponatremia can be transient and treatable.

The history of olanzapine use evoked for our patient a drug-related SIADH since both typical and the newer atypical anti-psychotic drugs have been accused [12-14]. Our patient however reported that she was not compliant with the Olanzapine treatment and that she did not use in the last months preceding the diagnosis of hyponatremia. Thus, iatrogenic SIADH was very unlikely.

Besides anti- psychosis, among other treatments reported causing hyponatremia, we find: anti-depressants, anti-epileptics, and anti-inflammatory drugs).

Multiple neurological (Guillain-Barré syndrome, subarachnoid hemorrhage, head trauma), infectious (tuberculosis, abscesses, meningitis, encephalitis), pulmonary (sarcoidosis, pneumonia, pneumothorax, asthma), and malignant causes (pulmonary, gastrointestinal, pancreatic, mesothelioma, sarcoma) can lead to SIADH [11].

Physical, biological and radiological assessment of our patient on admission showed no arguments in favor of one of these causes.

So, idiopathic SIADH was retained.

Therapeutic education of this patient should be carefully strengthened, the electrolytic and hemodynamic balance being made delicate by the association of the PAI and the SIADH.

Conclusion

Our case emphasizes the wide spectrum of causes of hyponatremia. A careful clinical evaluation of patients presenting with this problem, is imperative to guarantee adequate management. The diagnosis of acute adrenal crisis should be strongly evoked especially when having a familial or personal history of PAI, even when patient is euvolemic, but this diagnosis should not be hastily retained especially in the absence of other suggestive clinical and biological features. SIADH should be also evoked in patients with euvolemic hyponatremia and may be itself caused by several treatment and/or diseases. It's symptomatic treatment is usually simple and effective. A careful follow up should be offered to our patient since she has to limit her hydric intake while having chronic adrenal insufficiency. Till now, there is not known physiopathological relationship between SIADH and Allgrove syndrome.

Bibliography

1. Pintaldi S., *et al.* "SIADH versus adrenal insufficiency: a life-threatening misdiagnosis". *Italian Journal of Pediatrics* 45.1 (2019): 23.
2. Thompson MD., *et al.* "Severe hyponatraemia with absence of hyperkalaemia in rapidly progressive Addison's disease". *BMJ Case Report* (2015).

3. Chabre O., *et al.* "Epidemiology of primary and secondary adrenal insufficiency: Prevalence and incidence, acute adrenal insufficiency, long-term morbidity and mortality". *Annals of Endocrinology (Paris)* 78.6 (2017): 490-494.
4. Nasrallah F., *et al.* "X-linked Adrenoleukodystrophy, The Tunisian Experience". *Clinical Lab* 61.10 (2015): 1531-1536.
5. Sheikh MM and Bittar K. "Allgrove Syndrome". In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing (2020).
6. Kallabi F., *et al.* "Clinical and Genetic Characterization of 26 Tunisian Patients with Allgrove Syndrome". *Archives of Medical Research* 47.2 (2016): 105-110.
7. Derrar R., *et al.* "Alacrymie congénitale révélant un syndrome d'Allgrove: à propos de trois cas". *Pan African Medical Journal* (2015): 20.
8. Verbalis JG., *et al.* "Diagnosis, Evaluation, and Treatment of Hyponatremia: Expert Panel Recommendations". *The American Journal of Medicine* 126.10 (2013): S1-42.
9. Peri A. "Morbidity and Mortality of Hyponatremia". *Frontiers of Hormone Research* 52 (2019): 36-48.
10. Cuesta M and Thompson CJ. "The syndrome of inappropriate antidiuresis (SIAD)". *Best Practice and Research Clinical Endocrinology and Metabolism* 30.2 (2016): 175-187.
11. Tee K and Dang J. "The suspect – SIADH". *Australian Family Physician* 46.9 (2017): 677-680.
12. Kinjo T., *et al.* "Addison's disease due to tuberculosis that required differentiation from SIADH". *Journal of Infection and Chemotherapy* 15.4 (2009): 239-242.

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