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CASE REPORT

Acute behavioral disturbances and hyponatremia as the initial presentation of primary adrenal insufficiency

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Abstract

We present the case of a 12-year-old male who experienced a three-hour episode of fluctuating behavior, accompanied by a fever that began the previous day. There were no other significant symptoms or identifiable triggers. On examination, the patient showed a Glasgow Coma Scale score of 13-15, irritability, fluctuating incoherent speech and drowsiness, and skin hyperpigmentation. The remaining physical examination was unremarkable.

Given the acute behavioral changes, blood tests were ordered, revealing isolated hyponatremia with normal potassium levels. Urine electrolyte and toxicology studies were normal, PCR for SARS-CoV-2 was positive, brain CT scan showed no abnormalities, and lumbar puncture revealed normal biochemistry. Empirical treatment with cefotaxime and acyclovir was initiated, together with 3% hypertonic saline to correct symptomatic isolated hyponatremia of unknown etiology. A subsequent laboratory test revealed persistent hyponatremia and the onset of hyperkalemia, leading to the suspicion of an Addisonian crisis (AC). Consequently, stress-dose hydrocortisone was administered, resulting in both clinical and laboratory improvement. The initial laboratory tests revealed low cortisol levels and elevated ACTH, confirming AC, likely triggered by SARS-CoV-2 infection in a patient with underlying primary adrenal insufficiency (PAI). Further etiological studies identified positive anti-adrenal antibodies, confirming autoimmune PAI. The patient responded well to treatment with maintenance hydrocortisone and fludrocortisone and was discharged with outpatient follow-up.

Although PAI is a rare condition, it may lead to acute behavioral disturbances.

ALTERACIÓN AGUDA DEL COMPORTAMIENTO E HIPONATREMIA COMO DEBUT DE INSUFICIENCIA SUPRARRENAL PRIMARIA

Resumen

Se presenta el caso de un varón de 12 años con alteración del comportamiento fluctuante de tres horas, y fiebre iniciada el día anterior, sin otra sintomatología destacable ni claro desencadenante. Presenta una escala de Glasgow de 13-15, irritabilidad, discurso incoherente y somnolencia fluctuantes, e hiperpigmentación cutánea, con el resto de la exploración física anodina.

Dado el cuadro agudo de alteración del comportamiento, se solicita analítica sanguínea en la que solo destaca una hiponatremia aislada con potasio en rango, estudio de iones y tóxicos en orina que es normal, PCR para SARS-CoV-2 que es positiva, una TC craneal que no muestra anomalías, y se realiza una PL con bioquímica normal. Se administra tratamiento empírico con cefotaxima y aciclovir, y una corrección con suero

salino hipertónico al 3% por la hiponatremia aislada sintomática de etiología no filiada. En un control analítico posterior persiste la hiponatremia y aparece hiperpotasemia, orientándose como una crisis addisoniana (CA) por lo que se inicia tratamiento de estrés con hidrocortisona con mejoría clínico-analítica posterior. En el estudio realizado en la analítica inicial presenta niveles de cortisol bajos y ACTH elevado, confirmando la CA, probablemente desencadenada por infección por SARS-CoV-2 en un paciente con una insuficiencia suprarrenal primaria (ISRP) subyacente. En el estudio etiológico posterior presenta positividad para anticuerpos antiadrenales, confirmando una ISRP autoinmune. Mantiene buena evolución con hidrocortisona y fludrocortisona de mantenimiento, por lo que se da de alta con seguimiento ambulatorio.

La ISRP es una entidad poco frecuente pero que puede causar alteración aguda del comportamiento.

INTRODUCTION

Acute behavioral disturbances present a significant challenge for emergency pediatricians due to the wide range of differential diagnoses, including infectious, metabolic, neurosurgical, and psychiatric conditions, as well as their potential severity.

CASE REPORT

A 12-year-old boy was brought to the emergency department with a three-hour history of irritability, disorientation, fluctuating levels of somnolence, and fever with a maximum temperature of 38°C that began the previous day. He did not present with gastrointestinal symptoms, headache, coma, weakness, or any other notable symptoms. There was no reported exposure to drugs, toxins, or recent trauma.

His medical history included poor weight gain over the past two years, which was under investigation. A recent blood count was normal, but electrolytes were not measured, and an initial appointment with Endocrinology was pending. His vaccinations were up to date, except for SARS-CoV-2. There was no significant family history.

Upon initial examination, the patient had an altered Pediatric Assessment Triangle (PAT) with central nervous system dysfunction. Vital signs were as follows: heart rate 110 bpm, blood pressure 92/60 mmHg, oxygen saturation 99%, temperature 37.6°C, and blood glucose 107 mg/dl. Physical examination revealed a patent airway with no respiratory distress and normal pulmonary auscultation. Notable findings included mild skin hyperpigmentation, a capillary refill time of 2 seconds, a normal and rhythmic heart rate, and a Glasgow Coma Scale score fluctuating between 13 and 15. The patient showed irritability, incoherent speech, and fluctuating somnolence. Meningeal signs were negative, pupils were normoreactive, and no other significant alterations were observed.

Based on the above-described clinical features including acute behavioral disturbances and fever, possible causes (infectious, neurosurgical, metabolic, toxic, etc.) were investigated. A peripheral line was placed, and complete blood count, urine analysis with electrolyte and toxicology screen, and brain CT scan were requested. A volume load of 0.9% isotonic saline at 10 ml/kg combined with cefotaxime was administered, and treatment with acyclovir at 20 mg/kg was initiated. The initial laboratory tests (Table 1: Laboratory tests 1) showed only hyponatremia with normal potassium levels. A rapid repeat blood test was performed (Table 1: Laboratory Tests 2) to confirm the electrolyte findings and to further evaluate the neurological symptoms. Isolated hyponatremia was confirmed and classified as symptomatic hyponatremia of unidentified etiology, prompting correction with a 3% hypertonic saline solution (HSS) at 2 ml/kg. Urine analysis showed normal electrolyte levels and was negative for toxins. A brain CT scan was also normal. While awaiting the results of additional laboratory tests, a lumbar puncture (LP) was performed, which revealed normal biochemistry. Treatment with acyclovir and cefotaxime was continued until the microbiological studies returned negative results. Due to the fever and epidemiological history, a SARS-CoV-2 PCR was performed, which came back positive. Given the suspicion of SARS-CoV-2 encephalitis, remdesivir was administered until a negative SARS-CoV-2 PCR result was obtained from cerebrospinal fluid (CSF). Due to persistent and severe irritability, the patient was admitted to the ICU for sedation.

In the laboratory tests performed in the ICU after the administration of HSS (Table 1: Laboratory tests 3), persistent high sodium levels and newly elevated potassium levels were observed, raising suspicion of an Addisonian crisis (AC). As a result, hydrocortisone was initiated at a maximum stress dose of 100 mg/day. When discussing the suspected diagnosis with the family, they mentioned that over the last 2 years the patient had intense salt cravings and skin hyperpigmentation. After initiating hydrocortisone treatment, the neurological symptoms resolved and electrolyte levels normalized (Table 1: Laboratory Tests 4), and the patient was discharged to the ward. In a subsequent laboratory study conducted on the initial sample, low cortisol levels (4.2 µg/dl) and high ACTH levels (744 pg/ml) were found, confirming AC, likely triggered by a SARS-CoV-2 infection in a patient with primary adrenal insufficiency (PAI) or underlying Addison's disease. The etiological investigation of PAI included an abdominal CT, which showed normal adrenal glands, a negative PPD and QuantiFERON test, and positivity for anti-adrenal antibodies, confirming the diagnosis of autoimmune PAI. During his stay on the ward, the patient continued to show good clinical and laboratory progress while receiving hydrocortisone at a maintenance dose of 20 mg/m^2/day, fludrocortisone at 0.1 mg/

TABLE 1. Main laboratory parameters during the first 48 hours of admission .

Laboratory tests 1	Hb 14 g/dl, HCT 38.3%, PLT 217,000/mm^3, WBC 4,900/mm^3, LYMP 1,600/mm^3, NEUT 1,600/mm^3, PT 1.21, APTT 1.2, FIB 5.2 g/L, pH 7.36, pCO_2 36.1 mmol/L, HCO_3 19 mmol/L, EB -5 mmol/L, Na 122 mmol/L, K 4.3 mmol/L, Cl 85 mmol/L, Ca 1,25 mmol/L, Glu 81 mg/dl, Urea 31 mg/dl, Cr 0.6 mg/dl, ALT 24 UI/L, AST 45 UI/L, CRP 88 mg/L, PCT 0.4 ng/ml, LDH 2.5 mmol/L
Laboratory tests 2	Na 123 mmol/L, K 4.7 mmol/L, Cl 87 mmol/L, Ca 1.22 mmol/L
Laboratory tests 3	Na 121 mmol/L, K 6 mmol/L, Cl 91 mmol/L, Ca 1.19 mmol/L
Laboratory tests 4	Na 133 mmol/L, K 4.1 mmol/L, Cl 97 mmol/L, Ca 1.31 mmol/L

day, and stress doses as needed for intercurrent illnesses. As the patient evolved favorably, he was discharged with outpatient follow-up at the Endocrinology department and remained clinically and analytically stable.

DISCUSSION

Acute behavioral disturbances are of significant concern in pediatrics due to the potential morbidity and mortality associated with some etiologies. In the management of these cases, initial patient stabilization using the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach is a priority when an alteration in the PAT is found. Once stabilized, a correct medical history and detailed physical examination should be conducted[1]. Based on the suspected etiology, appropriate first-line diagnostic tests should be ordered (Table 2). Following the collection of these initial samples, empirical treatment—such as antibiotics, antivirals, and/or corticosteroids—should be initiated according to the suspected diagnosis and preliminary results. Additional second-line tests may include serology, specific antibodies, PCR, brain MRI, or EEG. Treatment should be adjusted based on definitive results[2].

Acute behavioral disturbances may be triggered by multiple causes (Table 3)[3,4]. One of the main etiologies is encephalitis, an inflammation of the brain parenchyma that may manifest clinically with fever, seizures, behavioral disturbances and altered mental status, CSF pleocytosis, changes on neuroimaging, and EEG alterations[5]. It can be caused by infectious agents, mainly viruses[2], or by autoimmune processes such as anti-NMDAR antibodies[6]. Among the viral etiologies of encephalitis, the SARS-CoV2 virus has been described to cause encephalitis through inflammatory, post-infectious, coagulopathic, or endothelial mechanisms, but not through direct neuropathogenesis of the virus[7].

Other causes of acute behavioral disturbance are hypoglycemia, and dyselectrolithemia (as in the case described) with hyponatremia (Na < 135 mmol/L) being the main cause in clinical practice. This can present with a wide range of predominantly neurological symptoms and be due to multiple causes (Figure 1). The treatment of hyponatremia will depend on the severity and etiology[8,9].

TABLE 2. First-line complementary examinations to perform in pediatric patients with acute behavioral disturbance.

- **Laboratory testing:** complete blood count, electrolytes, arterial blood gases, blood glucose, AST, ALT, GGT, bilirubin, coagulation profile, creatinine, urea, CRP, PCT, lactate
- **Blood culture**
- **Urinalysis:** sediment, electrolytes, toxins
- **Brain CT,** preferably with contrast
- **Lumbar puncture:** biochemistry, Gram stain, culture, PCR for HSV, pneumococcal and meningococcal testing

TABLE 3. Main causes of acute behavioral disturbance in pediatric patients.

- **Viral encephalitis:** HSV1, HSV2, VZV, EBV, CMV, HV type 6, enterovirus, adenovirus, parechovirus, JC virus, parotitis, HIV, SARS-CoV-2, rabies, Japanese encephalitis, Central European encephalitis, West-Nile virus, Dengue, Chikungunya
- **Bacterial meningitis:** *N. meningitidis, S. pneumoniae, S. agalactiae, L. monocytogenes, M. pneumoniae,* syphilis, rickettsiae, sepsis
- **CNS tuberculosis**
- **CNS protozoal infections:** malaria, toxoplasmosis
- **CNS fungal infections:** cryptococcosis, histoplasmosis
- **Autoimmune disorders:** anti-NMDAR, anti-LGI-1, anti-Hu, anti-Ma, anti-GAD, acute disseminated encephalomyelitis, Bickerstaff's encephalitis
- **Inflammatory causes:** vasculitis, systemic lupus erythematosus, Behçet's disease, neurosarcoidosis
- **Metabolic disturbances:** hypoglycemia, hepatic encephalopathy, adrenal insufficiency
- **Brain tumors:** primary brain tumor, metastasis
- **Brain hypoxia**
- **Brain hemorrhage**
- **Seizure-related:** status epilepticus, post-ictal state
- **Electrolyte imbalance:** hyponatremia, hypernatremia
- **Toxicity:** alcohol, recreational drugs, medications
- **Psychiatric disorder**

A potential cause of hyponatremia (hypovolemic or euvolemic) and acute behavioral disturbances is Addison's disease or PAI. In this condition, the destruction or dysfunction of the adrenal glands leads to a deficiency in adrenal hormones (glucocorticoids, mineralocorticoids, and/or androgens) that are crucial to maintain water and electrolyte balance, energy regulation, and sexual development[10]. Its manifestations include fatigue, weight loss, hyperpigmentation (due to a compensatory increase in ACTH), excessive salt intake, dehydration, hyponatremia (exceptionally associated with cerebral edema), and hypoglycemia[11]. In the context of an acute process, such as an infection, where an increased production of adrenal hormones is required, a potentially fatal condition known as an Addisonian crisis may be triggered[12]. In adults, the main etiology of PAI is autoimmune, primarily due to antibodies against the adrenal cortex and 21-hydroxylase[13], followed by tuberculosis; in children, the cause is genetic. Diagnosis requires low cortisol levels (< 5 µg/dl) and elevated ACTH levels (twice the upper limit

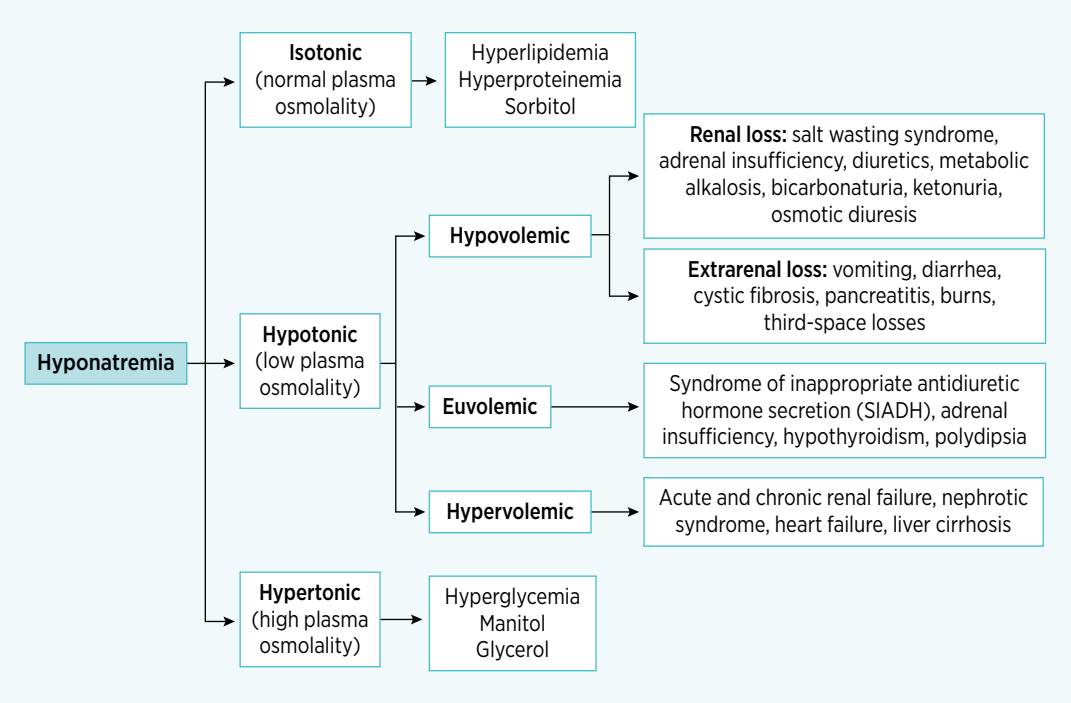

FIGURE 1. Classification of the potential causes of hyponatremia based on its characteristics.

for age) in a random sample taken before initiating glucocorticoid therapy. In addition, alterations in mineralocorticoids and/or androgens should be confirmed. Treatment consists of administering the deficient hormones and treating the underlying etiology, if possible[10,12].

Other potential causes of acute behavioral disturbances that should not be overlooked include the voluntary or accidental use of drugs or toxic substances[14], as well as psychiatric conditions[15].

COMMENTARY

This challenging case and its discussion aim to provide the reader with significant insight into the management of acute behavioral disturbance and a rare condition, PAI, requiring a high degree of suspicion.

STATEMENT OF THE AUTHORS

The authors declare no conflicts of interest related to this study. Informed consent was obtained from the legal guardian and is available for review. No external funding was received for this study.

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