A serious and unusual presentation of congenital isolated ACTH deficiency due to TBX19 mutation, beyond the neonatal period

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Summary

Congenital isolated adrenocorticotropic hormone (ACTH) deficiency due to T-box transcription factor-19 (TBX19 mutation) (MIM 201400; ORPHA 199296) usually presents in the neonatal period with severe hypoglycemia, seizures, and sometimes prolonged cholestatic jaundice. We report a case with an unusual presentation that delayed the diagnosis. A 9-month-old female patient with no relevant personal history was admitted to the emergency department due to a hypoglycemic seizure in the context of acute gastroenteritis. There was rapid recovery after glucose administration. At age 4, she presented with tonic-clonic seizures, fever, and gastrointestinal symptoms and came to need support in an intensive care unit. Low serum cortisol was documented and hydrocortisone was initiated. After normalization of inflammatory parameters, the patient was discharged with hydrocortisone. The genetic investigation was requested and compound heterozygous mutations in TBX19 were detected. This is a rare case of presentation of TBX19 mutation outside the neonatal period and in the setting of acute disease, which presented a diagnostic challenge.

Learning points:

- Congenital isolated adrenocorticotropic hormone deficiency due to TBX19 mutation usually presents with neonatal hypoglycemia and prolonged cholestatic jaundice.
- An uneventful neonatal period, however, does not exclude the diagnosis as the disease may be asymptomatic at this stage.
- In the context of idiopathic hypoglycemia, even in the context of acute disease, hypocortisolism must always be excluded.
- Genetic evaluation should be performed in cases of congenital central hypocortisolism to allow proper counselling.

Background

Hypoglycemia is a relatively common finding during pediatric age. The main causes can be divided into several groups: innate metabolism errors, ketotic hypoglycemia, endocrine disorders, and drug-induced and factitious hypoglycemia (1). The deficiency of counterregulatory hormones represents a rare cause of hypoglycemia, which can present as intolerance to fasting, more frequent in infants and young children (2). Cortisol is one of the hormones that contribute to glucose homeostasis. Hypocortisolism may present with hypoglycemia accompanied by symptoms such as fatigue, anorexia, nausea and vomiting, weight loss, abdominal pain, weakness, decreased pubic and axillary hair, hypotension, dehydration, and altered mental status (1). However, persistent neonatal hypoglycemia may be
the only manifestation (3). The pituitary-restricted T-box transcription factor-19 (TBX19), previously known as TPIT, is an essential transcription factor for the differentiation of cells expressing pro-opiomelanocortin (POMC). Mutations in this gene are responsible for most cases of isolated adrenocorticotropic hormone (ACTH) deficiency (IAD) presenting in the neonatal period (4).

Case presentation

We present a case of a 9-month-old female infant, born from a 41-week gestation with adequate prenatal care. The birth weight was 4220 g (z-score 0.85 s.d.), height was 52.5 cm (z-score 0.3 s.d.), and the head circumference was 37 cm (z-score 0.7 s.d.). During the neonatal period, the persistence of the ductus arteriosus and possible interatrial communication were detected and treated with oral ibuprofen. No other abnormalities were found during the first month of life, including episodes of hypoglycemia or jaundice. The parents were not consanguineous and there was no family history of sudden or early death, genetic disorders, autoimmune diseases, or intellectual deficit.

The infant was admitted to the emergency department due to a hypoglycemic seizure during an episode of acute gastroenteritis. The initial assessment showed that the hypoglycemia was associated with high ketonemia (1.3 mmol/L) that was assumed to be in the context of gastrointestinal symptoms, the infant was admitted for surveillance. During hospitalization, she exhibited a favorable clinical evolution, without new episodes of hypoglycemia. Due to the rapid resolution of the episode, the child was discharged with recommendations for regular feeding and capillary blood glucose monitoring before meals.

In the following 3 years, there was a single episode in which capillary blood glucose < 55 mg/dL was detected, in the context of acute bronchiolitis, and with no associated symptoms. She presented with other episodes of bronchiolitis without documented hypoglycemia, and therapy with inhaled fluticasone was initiated. The patient maintained an adequate height and weight development, although always in high percentiles (P97). A predominantly motor delay was detected, with difficulty in walking. A slight delay in speech was also suspected at 2 years of age, but she was able to communicate and interact adequately with her parents and peers.

When she was 4 years of age, the patient presented with a generalized tonic-clonic seizure, fever, and diarrhea lasting less than 24 h.

Investigation

Initial evaluation was performed according to the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach. The patient was febrile (38.5°C axillary temperature), hemodynamically unstable, with anuria, and scoring 8 on the Glasgow Coma Scale and dropping rapidly to 5. A summary neurological examination was performed, revealing a conjugated gaze deviation to the right. Venous blood samples were collected and the first laboratory tests showed capillary blood glucose to be 43 mg/dL, and elevated inflammatory parameters – leukocytosis with neutrophilia, C-reactive protein – to be 64 mg/dL (<10), and procalcitonin to be 84 ng/mL (<0.5). An arterial blood gas sample was also collected and revealed metabolic acidosis.

Treatment

Dextrose perfusion was started, and the patient was submitted to endotracheal intubation and ventilation and transferred to the intensive care unit. Antibiotic therapy was initiated with i.v. ceftriaxone and flucloxacillin; however, no etiological agent was identified in blood, stool, and urine cultures. Due to refractory hypoglycemia, i.v. stress dose of hydrocortisone was also initiated.

During hospitalization, the clinical course was unfavorable, evolving to multiorgan failure and disseminated intravascular coagulation, requiring maintenance of invasive ventilation and inotropic support. After extubation and discontinuation of sedatives, the infant persisted with altered mental status, agitation, hypertonia, doubts about eye contact, spontaneous and adequate mobility of the four limbs, and also many involuntary movements. Cranioencephalic CT performed at admission revealed a bilateral parietotemporal acute hypoxic-ischemic insult. On the fourth day, the imaging examination was repeated revealing cortico-subcortical hypodensities of the posterior arterial territories in both hemispheres. The MRI performed on the eighth day showed brains lesions, which considering the clinical history and the preferential posterior cortical involvement, might be related to severe hypoglycemia and, possibly, with hypoxic-ischemic lesions (Fig. 1). The hormonal evaluation (using chemiluminescent immunoassays) showed high thyroid-stimulating hormone (TSH) and free thyroxine (fT4) within the reference ranges and negative antithyroid antibodies, excluding Hashimoto’s encephalopathy. Cortisol < 1.0 μg/dL and ACTH < 5.0 pg/mL were found in the context of hypoglycemia (Table 1). The ketone bodies in urine were positive and the 3-hydroxybutyrylcarnitine was significantly increased and the...
propionylcarnitine slightly increased. After resolution of the infectious condition, she was discharged medicated with hydrocortisone 2.5 mg 8/8 h, levothyroxine 12.5 μg i.d., and anticonvulsants. During subsequent investigation, organic acid and acylcarnitine profiles were repeated with no significant alterations. Given the low cortisol and ACTH values, ketotic hypoglycemia, and severe hypotension, the diagnosis of hypocortisolism of pituitary origin was made.

Outcome and follow-up

The patient was referred to our Genetics Department and a whole exome sequencing with copy number variation (CNV) analysis was performed, which identified, in heterozygous state, the variants NM_005149.2: c.299G>A p.(Arg100His) and NM_005149.2: c.856C>T p.(Arg286*) in the TBX19 gene. Both variants are classified as pathogenic and were previously described in the literature and the ClinVar as associated with congenital isolated ACTH deficiency, a rare autosomal recessive disorder. Both parents were heterozygous for one of the mutations, and this result confirms that variants are in compound heterozygosity (in trans) in the patient.

After discharge, the patient maintained therapy with hydrocortisone and anticonvulsants. There were no new episodes of hypoglycemia; however, she had multiple infectious respiratory complications, and non-invasive mechanical ventilation was started at night.

Currently, the child is 12 years old, can walk autonomously although with some difficulties, smiles, and can follow with her gaze, but does not verbalize. She has had regular pubertal development, with the onset of menarche at 11 years and 10 months, and is currently at Tanner Stage 3. She has been maintained under a multidisciplinary follow-up in endocrinology, metabolic diseases, neurodevelopment, physiatrics, and pulmonology consultations, and attends rehabilitation and occupational therapy program.

The autosomal recessive heredity with a 25% recurrence risk in future pregnancies was explained to the parents and the available reproductive options were discussed, namely molecular prenatal diagnosis and preimplantation genetic test.

Discussion

The development of the pituitary gland is complex and coordinated by a cascade of signaling molecules and transcription factors (5). TBX19 is essential for the expression of the POMC gene (4, 5) of the corticotropic lineage (6).

Congenital adrenal insufficiency is a life-threatening condition and may be primary (alteration in the adrenal gland), secondary (ACTH deficiency), or tertiary (corticotropin-releasing hormone (CRH) deficiency). It usually presents with severe hypoglycemia, seizures, and sometimes with prolonged cholestatic jaundice in the neonatal period. Nonspecific symptoms may include lethargy, feeding difficulties, fatigue, hypotension, and vomiting. In children, recurrent infections are also a form of presentation (6, 7). A partial insufficiency may go unnoticed and present with shock with good response to hydrocortisone (6). TBX19 mutations account for 60% of cases of neonatal onset adrenal insufficiency (4). Heredity is autosomal recessive, with homozygous or compound heterozygous individuals expressing the disease. In a series of 91 patients with IAD, Couture et al. described 21 different TBX19 mutations (4); however, new mutations have been identified since (7, 8).

A high prevalence of neonatal mortality was found in families with these mutations, which may correspond to an
underestimated cause of neonatal mortality (5). Hormonal
evaluation is usually characterized by very low cortisol and
ACTH, without abnormalities in the remaining axis
(9). However, an association has been reported between
transient growth hormone and TSH deficiency (10). MRI is
consistently described as normal (4). We present a case of congenital ACTH deficiency
caused by TBX19 mutation with an extremely rare
presentation, without hypoglycemia, jaundice, or feeding
difficulties in the neonatal period, and with normal
thiving. Even though some causes of congenital ACTH
deficiency can have a late presentation, in published series
of patients with ACTH deficiency due to TBX19 mutation,
homogeneity was described in the presentation with
neonatal hypoglycemia in all and prolonged cholestatic
jaundice in the majority (4, 9). One previous case report
differs from this pattern, with presentation during infancy
with recurrent respiratory tract infections (7).

The initial presentation of hypoglycemia during an
episode of acute disease, with rapid resolution, led to
the hypothesis of hypocortisolism not initially being
investigated. Treatment with inhaled corticosteroids may
also have contributed to reduce disease manifestations
during the following years. It is likely, however, that other
unrecognized episodes of hypoglycemia have occurred
during the child’s development, thus contributing to her
developmental delay.

Hypocortisolism is a rare but severe cause of
hypoglycemia. This pathology may not be evident in the
neonatal period; however, the presence of hypoglycemia
with documented Whipple triad, or blood glucose
levels < 60 mg/dL in children unable to express symptoms,
should always motivate a cortisol measurement in
hypoglycemia. If this is not possible, especially in case of
recurrence or severe symptoms, consideration should be
given to conducting a stimulation test. If this hypothesis
of diagnosis is being considered, however, hydrocortisone
administration should not be delayed and the study can be
concluded later in a more controlled environment. Genetic
evaluation should be performed in cases of congenital
central hypocortisolism, as to identify hereditary causes
and allow proper counselling.

Declaration of Interest
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Author contribution statement
I V and N B M produced the report and performed the literature review.
F S, I D, R C, J S C and D R assisted in the production of the report and
the literature review. A M and I P oversaw the creation of the report and
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