Endocrinology, Diabetes & Metabolism CASE REPORTS

I H Vieira and others

ID:22-0277;September2022
DOI: 10.1530/EDM-22-0277

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

Inês Henriques Vieira[1], Nádia Mourinho Bala[2], Fabiana Ramos[3], Isabel Dinis[4], Rita Cardoso[4], Joana Serra Caetano[4], Dírcea Rodrigues[1], Isabel Paiva[1] and **Alice Mirante[4]**

[1]Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar e Universitario de Coimbra EPE, Coimbra, Portugal, [2]Department of Endocrinology, Diabetes and Metabolism, Hospital Beatriz Ângelo, Loures, Portugal, [3]Department of Medical Genetics, and [4]Department of Endocrinology, Diabetes and Growth, Centro Hospitalar e Universitario de Coimbra EPE, Coimbra, Portugal

Correspondence should be addressed to I H Vieira
Email
nafnici@gmail.com

Summary

Congenital isolated adrenocorticotrophic 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 adrenocorticotrophic 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

ID:22-0277;September 2022
DOI: 10.1530/EDM-22-0277

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 adrenocorticotrophic 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 gastroenteritis. Given the presence of hypoglycemia associated with 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

ID:22-0277;September 2022
DOI: 10.1530/EDM-22-0277

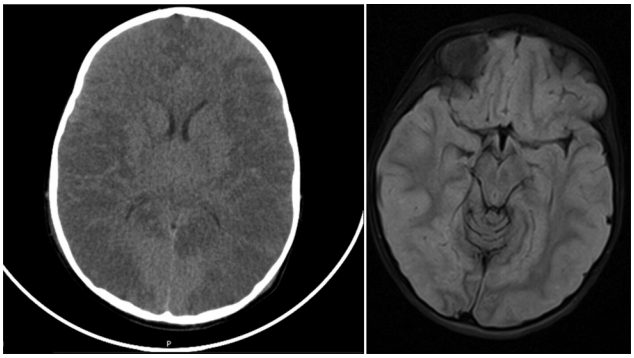

Figure 1
CT scan (on the left) revealing diffuse cortical hypodensities translating hypoxic-ischemic encephalopathy. MRI scan (on the right) revealing extensive cytotoxic cortical edema.

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 autosome 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.

Table 1 Patient's hormonal study.

	Value	Reference range
Results during hospitalization for the acute episode		
Glucose, mg/dL	39	
ACTH, pg/mL	<5	<46
Cortisol, µg/dL	<1.0	5.0–25.0
TSH, mIU/L	7.28	0.7–4.17
fT4, ng/dL	1.2	0.8–1.57
IGF-1, ng/mL	55 n	40–154
Insulin, µIU/mL	<2.0	6.0–27.0
Results during follow-up appointments*		
Prolactin, ng/mL	7.4	4.2–23
FSH, mIU/L	5.7	<9.6
LH, mIU/L	4.3	<12
Estradiol, pg/mL	13	10–200

*For these parameters, we present the study collected more recently after menarche, the reference ranges for the follicular phase are presented for FSH, LH, and estradiol.

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 thriving. 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
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this case report.

Funding
This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Patient consent
Written informed consent for publication of their clinical details and clinical images was obtained from the parent of the patient.

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 was involved in the care of the patient. All the authors approved the final version to be published.

References

1 Hoe FM. Hypoglycemia in infants and children. *Advances in Pediatrics* 2008 **55** 367–384. (https://doi.org/10.1016/j.yapd.2008.07.008)
2 Cryer PE & Arbelaez AM. Hypoglycemia. In *Williams Textbook of Endocrinology*, 14th ed., pp. 1913–1947. Elsevier, 2020.
3 Mehta S & Brar PC. Severe, persistent neonatal hypoglycemia as a presenting feature in patients with congenital hypopituitarism: a review of our case series. *Journal of Pediatric Endocrinology and Metabolism* 2019 **32** 767–774. (https://doi.org/10.1515/jpem-2019-0075)
4 Couture C, Saveanu A, Barlier A, Carel JC, Fassnacht M, Flück CE, Houang M, Maes M, Phan-Hug F, Enjalbert A, *et al.* Phenotypic homogeneity and genotypic variability in a large series of congenital isolated ACTH-deficiency patients with TPIT gene mutations. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** E486–E495. (https://doi.org/10.1210/jc.2011-1659)
5 Kelberman D & Dattani MT. Hypothalamic and pituitary development: novel insights into the aetiology. *European Journal of Endocrinology* 2007 **157** (Supplement 1) S3–S14. (https://doi.org/10.1530/EJE-07-0156)
6 Patti G, Guzzeti C, Di Iorgi N, Maria Allegri AE, Napoli F, Loche S & Maghnie M. Central adrenal insufficiency in children and adolescents. *Best Practice and Research: Clinical Endocrinology and Metabolism* 2018 **32** 425–444. (https://doi.org/10.1016/j.beem.2018.03.012)
7 Akcan N, Serakıncı N, Turkgenc B, Bundak R, Bahceciler N & Temel SG. A novel TBX19 gene mutation in a case of congenital isolated adrenocorticotropic hormone deficiency presenting with recurrent respiratory tract infections. *Frontiers in Endocrinology* 2017 **8** 64. (https://doi.org/10.3389/fendo.2017.00064)
8 Weijing K, Liping Z, Tiantian Z, Pei Z & Yan M. A case of congenital isolated adrenocorticotropic hormone deficiency caused by two novel mutations in the TBX19 gene. *Frontiers in Endocrinology* 2019 **10** 251. (https://doi.org/10.3389/fendo.2019.00251)
9 Vallette-Kasic S, Brue T, Pulichino AM, Gueydan M, Barlier A, David M, Nicolino M, Malpuech G, Déchelotte P, Deal C, *et al.* Congenital isolated adrenocorticotropin deficiency: an underestimated cause of neonatal death, explained by TPIT gene mutations. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 1323–1331. (https://doi.org/10.1210/jc.2004-1300)
10 Jullien N, Saveanu A, Vergier J, Marquant E, Quentien MH, Castinetti F, Galon-Faure N, Brauner R, Turki ZM, Tauber M, *et al.* Clinical lessons learned in constitutional hypopituitarism from two decades of experience in a large international cohort. *Clinical Endocrinology* 2021 **94** 277–289. (https://doi.org/10.1111/cen.14355)

Received in final form 1 August 2022
Accepted 18 August 2022