TPIT mutation may be involved in multiple pituitary deficiencies

A clinical case

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Congenital hypopituitarism must be mentioned in case of hypoglycemia, microphallus, undescended testes, prolonged jaundice. When hypopituitarism is diagnosed, MRI is necessary to assess the pituitary morphology. Differents genes can be involved and have to be screnned for the molecular diagnosis (PROP1, LHX3, HESX1, POU1F1, PITX1, PTX2, OTX2, SOX2, SOX3).

CLINICAL CASE

The patient was the couple's first child. Parents were first cousins. The boy was delivered at 37 weeks of gestation, with birth weight of 2750g, birth length of 46,6cm and head circumference of 33,5cm.
Clinic He had immediate hypotonia, poor feeding, hypoglycemia, and early jaundice. External genitalia was normal.
Biology Blood glucose was 1,65mmol/L, total bilirubin was 300µmol/L, unconjugated bilirubin was 260µmol/L and gamma-glutamyl transpeptidase were 186UI/L. Pituitary and/or adrenal insufficiencies were suspected (Table 1).

GH,ACTH and TSH deficiencies were diagnosed.

Treatment hydrocortisone, growth hormone and thyroid hormone treatments were started which allowed for a rapid improvement of hypotonia, jaundice and blood glucose.

Pituitary MRI was normal.

Genes involved in multiple pituitary hormone deficiences were screened (Table 2).

	Patient	Reference range for age (2)
ACTH	< 1,0 ng/L	5 - 49
Cotisol	1µg/L	18 - 252
DHEA-S	53 nmol/mL	360 - 2000
TSH (1)	3,10 mUI/L	1,18 – 3,57
FT4 (1)	14,40 pmol/L	15,91 – 31,65
IGF1	21 ng/mL	45 - 150
IGFBP3	0,9 mg/L	1,2 - 3
GH	7,60 ng/mL	7 - 30

Table 1.

Table 2.

Screneed genes	Mutation
Prop 1	no
LHX 3	no
T-PIT (TBX19)	Homozygous mutation c.383C>A (p.Ser128Tyr)

TPIT was screened because the symptoms of adrenocorticotropic deficiency were predominant an hydrocortison allowed a spectacular improvement.

DIAGNOSIS

Congenital isolated adrenocorticotropic hormone (ACTH) déficiency is a rare condition that was first reported in 1954 (3) and could be an underestimated cause of neonatal death. It is characterized by low plasma ACTH and cortisol levels and preservation of all other pituitary hormones. The principal molecular cause is identified as TPIT (TBX19) mutation (4). TPIT is a highly cell-restricted transcription factor that is required for the expression of the propiomelanocortin (POMC) gene and for terminal differentiation of the pituitary corticotroph lineage (5).
The largest series published up to now comprised 91 patient with isolated ACTH deficiency (IAD) by C. Couture *et al* in 2012. In this study, 22 patients had chilhood ACTH deficiency (none had TPIT mutation), and 69 had neonatal onset. Among the 69 patients with neonatal-onset, 57 had complete ACTH deficiency. TPIT gene mutation were found in 37 of 57 patients with complete neonatal IAD. The patients were homozygous or compound heterozygous for TPIT mutation and their parents were healty heterozygous carriers (4). Two patients had partial and transient GH deficiency.

CONCLUSION

Hypoglycemia associated with an endocrine deficiency is usually due to adrenal insufficiency with or without growth hormone deficiency (3). The symptoms fo our child are the same described in congenital early onset isolated ACTH deficiency. It is important to know this signs because the treatment is simple and a late diagnosis can lead to neonat death. In our patient,initial hormonal evaluation suggested combined growth hormone and TSH deficiency which are not usually described in TPIT mutation.

TAKE HOME MESSAGE

Multiple pituitary hormone deficiencies with corticotropin deficiency may lead to the molecular diagnosis of TPIT mutation.

Referencess : 1- Annemieke J.Lem, JCEM 2012 ; 2- Normes néonatales Robert-Debré ; 3- Luu-Ly Pham, Plos ONE, 2011 ; 4- C Couture, JCEM 2012 ; 5- B Atassay, Journal of Pediatric Endocrinology and Metabolism 2004

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