CASE REPORT: Hypothyroidism and ACTH-deficiency caused by TBX19 mutation. Coincidence or pathogenetic correlation?
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Background: Congenital isolated ACTH-deficiency is a rare disorder characterized by low plasma ACTH and cortisol levels and normal secretion of other pituitary hormones. TBX19 is a t-box transcription factor with a specific role in the differentiation of corticotroph cells. TPIT gene mutations can be found in early onset isolated ACTH deficiency

Clinical case: (there is informed consent on showing clinical data):
- 2.3 year old girl admitted for further endocrinological evaluation because of hypocortisolism, hypothyroidism and tall stature

Former history:
- Birth at 40 weeks of gestational age (birth weight: 2500g, length: 50 cm), first child of consanguineous parents
- Severe hypoglycemia at the first day of life, no further hypoglycemias during neonatal period, tube feeding due to muscular hypotonia during the first 3 weeks
- Prolonged jaundice and cholestasis in combination with striking facial symmetric features led to further investigation (age 3 weeks)

Laboratory results:
- Normal values for:
  - Total bilirubin: 15.19 mg/dL (con. bilirubin: 1.29 mg/dL)
  - gGT: 470 IU/L (6-42)
  - ASAT (GOT): 31 IU/L (≤32)
  - ALAT (GPT): 8 IU/L (≤31)
  - Amphion: 154 μg/dL (19-62)

Normal ultrasonography of abdomen, heart and brain

No diagnosis could be made, cholestasis normalized at the age of 6 months

Hypothyroidism revealed at the age of 8 months during follow up, delayed psychomotor development was observed:
- TSH: 12.09 μIU/mL (0.4-4.7)
- FT4: 0.68 ng/dL (0.85-1.8)

Severe hypoglycemia (BG: 22 mg/dL; 1.22 mmol/L) with prolonged epileptic seizure at the age of 20 months: EEG: Sharp-wave-complexes on left side, cMRI: scan: Normal pituitary gland, Treatment: Sulfamid

Diagnosis of hypocortisolism at the age of 24 months:
- Cortisol: <10 μg/dL, ACTH: >5 ng/L
- Hydrocortisone (13 mg/m²) was started, further endocrinological evaluation planned

Physical examination at 2.3 years:
- Dysmorphic facial features (synophrys with long curved eyebrows, inclined axis of eyelid, low set ears, deep hairline)
- Infantile female external genitals
- Body length: 94.2 (+1.3 SD)
- Body weight: 14.6 kg
- BMI: 16.4 kg/m²
- Target height: 156 (-2.2 SD)
- HTSDS-THSDDS: +2.2 SD
- Bone age: 16 months accelerated

Conclusion:
- Isolated ACTH deficiency is a rare disease and an important differential diagnosis of congenital hypothyroidism
- TPIT gene mutations may be found in early onset IAD, the delayed diagnosis in the reported girl does not conflict the early onset form of IAD

Endocrinological investigation:

Analysis of multilistertic hormones:
(determined in plasma with liquid chromatography tandem mass spectrometry (LC-MS/MS))
- Progesterone <0.3 ng/mL (0.04-0.43)
- 11-Desoxycorticosterone 0.06 ng/mL (0.06-0.56)
- Corticosterone 0.2 ng/mL (0.09-2.5)
- 17-OH-Dehydroepiandrosterone <0.3 ng/mL (0.06-1.62)
- 17-OH-Dehydroepiandrosterone 0.06 ng/mL (0.06-0.67)
- 11-Desoxycorticisold 0.03 ng/mL (0.09-1.96)
- 21-Desoxycorticisold 0.14 ng/mL (0.04-1.63)
- DHEAS 1.7 ng/mL (15-71)
- Cortisone 0 ng/mL (1.93-33.89)
- Cortisold 1.7 ng/mL (7.8-159.08)

Cortisol profile:
- Time 8 am 2 pm 6 pm
- Cortisol ng/mL (43-224)
  - 2.6
  - 28.1
  - 104.4
- ACTH pg/mL (4.7-48.8)
  - 1.9
  - 1.9
  - 4.1

CRH-Test:
- Time (minutes) 0 +15 +30 +45 +60
- Cortisol ng/mL <2 <2 <2 <2 <2
- ACTH pg/mL 5.0 3.4 2.8 6.0 2.7

Molecular genetic investigation of TBX19 Gene:
Homogygosity for c.865C>T (p.Asp286Val), exon 6, stop-mutation in exon 6, previously reported in literature 2001 by Lamott (2) in patients with congenital ACTH deficiency

Congenital isolated ACTH-deficiency and TBX19 mutation:
- TPIT (TBX19) encodes a t-box transcription factor, that is essential for cell-specific transcription of the POMC gene in the pituitary and for differentiation of corticotroph cells (2)
- TPIT mutations lead to congenital isolated ACTH deficiency (IAD) and may be found in early onset forms of IAD (3,5)

Hypothyroidism in isolated ACTH deficiency:
- None of the previously reported patients with IAD caused by TPIT mutations are given account to have abnormal thyroid function (4,5)
- Two previously reported patients presented transient growth hormone deficiency (4,5)
- Transient hypothryoidism in patients with isolated ACTH deficiency has been reported (6), mainly in adults
- Different mechanisms of thyroid dysfunction due to hypocortisolism are assumed: missing suppressive effect of glucocorticoids on TSH secretion (7), impaired synthesis or secretion of thyroid hormone under stimulation of TSH during hypocalciosism (6)
- It is recommended to reassess thyroid function after replacement of hydrocortisone (6)

Diagnosis may be delayed although neonatal hypoglycemia, prolonged jaundice due to cholestasis and muscular hypotonia are characteristic symptoms of congenital hypocortisolism

Hypothyroidism may appear in nonreversed hypocortisolism and be transient
Reassessment of thyroid function after replacement of hydrocortisone should be performed to prevent unnecessary substitution of thyroid hormone

Literature:
1. Looitink, K.P. et al.: Small thyroid volumes and normal iodine excretion in Berlin schoolchildren indicate full normalization of iodine supply. Experimental & Clinical Endocrinology & Diabetes 1999; 106: G45-G50