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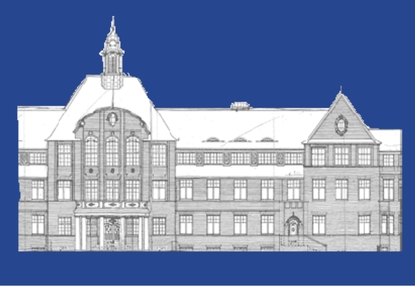

CASE REPORT: Hypothyroidism and ACTH-deficiency caused by TBX19 mutation. Coincidence or pathogenetic correlation?

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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 evaluaton 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 syndromic features led to further investigation **(age 3 weeks):**

Laboratory results:	**Normal results for:**
Total bilirubin 15,19 mg/dl	TSH, fT4, fT3
(conj. bilirubin 1,29 mg/dl)	Neurometabolic lab. tests
gGT 470 U/l (6-42)	Alpha-1- antitrypsin
ASAT (GOT) 31 U/l (<32)	Connatal infections (TORCH)
ALAT (GPT) 8 U/l (<31)	Chromosomal analysis: 46 XX
Ammonia 154 µg/dl (19-82)	Array-CGH

  - Normal ultrasonography of abdomen, heart and brain

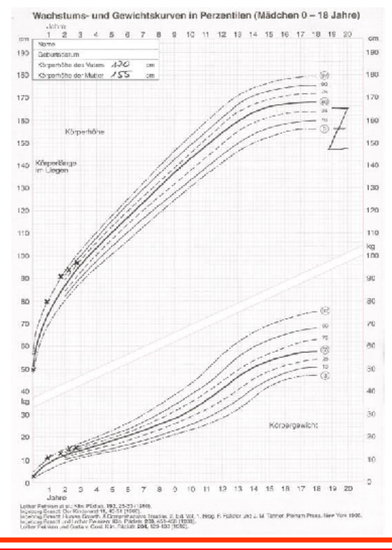
    No diagnosis could be made, cholestasis normalized at the age of 6 months
  - **Hypothyroidism** revealed at the age of **8 months** during follow up, delayed psychomotor development was observed:
    - TSH 12,09 µIU/ml (0,4-7)
    - fT4 0,68 ng/dl (0,85-1,8)

    Ultrasonography of thyroid (2;3 y):
    Loco typico, volume: 0,5 ml (N: 1,5 ml +/- 1,4 (1))
  - **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: Sultiam
  - **Diagnosis of hypocortisolism** at the age of **24 months**:
    - **Cortisol <10µg/l, ACTH <5 ng/l**

      Hydrocortisone 13 mg/m² bsa 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-THSDS: +2,2 SD**
  - Bone age: 16 months accelerated



Endocrinological investigation:

Analysis of multisteroid hormones:

(determinated 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-Pregnenolone <0,3 ng/ml (0,06-1,62)
- 17-OH-Progesterone 0,06 ng/ml (0,06-0,57)
- 11-Desoxycortisol <0,03 ng/ml (0,09-1,95)
- 21-Desoxycortisol 0,14 ng/ml (0,04-1,63)
- DHEAS 1,7 ng/ml (15-71)
- Cortisone 0 ng/ml (1,93-33,89)
- Cortisol 1,7 ng/ml (7,8-159,08)
- Aldosterone 161 ng/l (11,7-236)
- Renin 21,5 ng/l (1,6-22,3)
- FSH 3,4 mIU/ml, LH<0,3 mIU/ml
- TSH 0,49 µIU/ml (0,54-4,2)
  (medication: levothyroxine 40 µg/d)
- fT3 3,5 pg/ml (2-6)
- fT4 1,51 ng/dl (0,9-1)
- Prolactine 12,9 ng/ml (2,5-20)
- IGF1 127 ng/ml (P83,4)
- IGF BP3 3,6 µg/ml (P99,3)

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:**
  Homozygosity for c.856C>T (p.Argin286*), exon 6, stop-mutation in exon 6, previously reported in literature 2001 by Lamolet (2) in patients with congenital isolated ACTH deficiency

Congential 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 hypothyroidism 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 hypocortisolism (6)
- It is recommended to reassess thyroid function after replacement of hydrocortisone (8)

Conclusion:

- Isolated ACTH deficiency is a rare disease and an important differential diagnosis of congenital hypocortisolism
- 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 isolated IAD
- 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 nontreated hypocortisolism and be transient
- Reassessment of thyroid function after replacement of hydrocortisone should be performed to prevent unnecessary substitution of thyroid hormone

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