Case report: Neonatal McCune-Albright syndrome with juvenile ovarian granulosa cell tumor in a 4 months old girl

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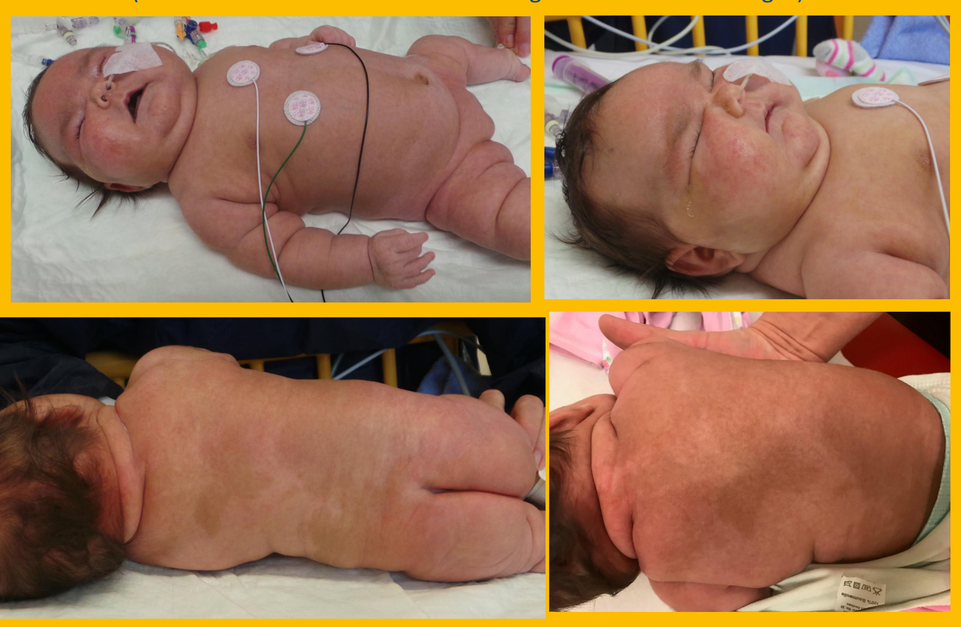
Introduction: McCune-Albright syndrome (MAS) is a rare disease resulting from a somatic activating mutation of GNAS1 encoding the Gs-alfa subunit of the G-protein coupled membrane receptor responsible for multiple hormonal signaling cascades leading to the classical trias: polyostotic fibrous dysplasia, café-au-lait hyperpigmentation and GnRh independent precocious puberty. Early manifestation is accompanied by multiple organ involvement and may lead to ACTH-independent hypercortisolism, hyperthyroidism, cardiac alterations, hepatopathy and GH-Excess in addition to the classical trias.

Girl at age of 6 weeks:

(there is informed consent on showing clinical data and images)

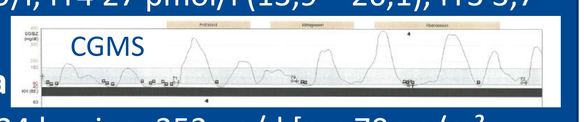


History:

- 2. child, uneventful pregnancy, delivery at 37 weeks of gestational age, birth weight 3505 g, length 52 cm, head circumference 34 cm
- Polydipsia since birth (up to 2 l/day at age of 5 weeks)
- At the age of 5 weeks: weight 4000 g, length 50 cm, h.c. 34 cm
- Further investigation because of heart murmur

Clinical findings and course:

- **Hypertrophic obstructive cardiomyopathy** (LVEDD 14 mm),
- **Hyperthyroidism** (TSH <0,02 mU/l, fT4 27 pmol/l (13,9 – 26,1), fT3 3,7 pmol/l (4,5 – 10,5)
- **Glucosuria and hyperglycemia**



- **Hypercortisolism** (free Cortisol 24 h urine: 353 µg/d [n < 70 µg/m² body surface], ACTH <5 µg/l, Cortisol i.S.: 338– 370 µg/l without diurnal rhythm)
- **Hepatopathy** (GOT 118U/l, GPT 411 U/l, yGT 2078 U/l, Bili 2,1 mg/dl)
- **Autonomous ovarian cysts** (Ultrasound: Volume ovary left 11 ml, right 4,7 ml, cysts with max. diameter of 2,6 cm, LH < 0,3 mIU/ml, FSH < 1,7 mIU/ml, estradiol: 108 pg/ml)
- **Nephrocalcinosis** (Ca ion. 1,56 mmol/l, Phos. 1,11 mmol/l, Ca/Kreat Ratio: 0,98 mg/mg, TPR: 76,1%, FGF 23: 195 kRU/l [n 26-110])
- **Polyostotic fibrous dysplasia**
- **Therapy: Effective treatment of hypercortisolism with metyrapone** (see table 1) **and the side effect of excessive hyperandrogenemia** (see table 2)

Effective treatment of hypercortisolism with metyrapone (150-150-150 mg):

TMS-steroid profile (cap. blood) before and 4 h after metyrapone:

Table 1

Hours	9 am	*1 pm **	5 pm	*9 pm **	1 am	*5 am **
Cortisol ng/ml	59,4	*23,9*	89,5	*29*	55	*15,6*

* = 4 h after metyrapone

Excessive hyperandrogenemia during therapy with metyrapone:

Table 2

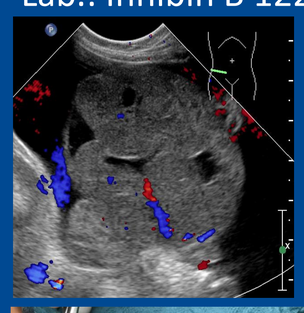
Hormone	before metyrapone	during metyrapone	min.	max.	unit
Progesterone	1,51	**3,24**	0,04	9,56	ng/ml
11-Desoxycortiscosterone	0,1	**1,9**	0,05	0,47	ng/ml
Corticosterone	1,9	**<0,3**	0,09	8,01	ng/ml
Aldosterone		**0,09**	0,03	0,82	ng/ml
17-OH-Pregnenolone	7,4	**84,5**	1,68	23,8	ng/ml
17-OH Progesterone	**1,68**	**3,49**	0,06	1,33	ng/ml
11-Desoxycortisol	0,39	**47,78**	0,09	2,35	ng/ml
21-Desoxycortisol	<0,03	**<0,03**	0,04	0,93	ng/ml
Cortisol	**221,7**	**36,7**	7,47	128,66	ng/ml
Cortisone	**59**	**24**	5,77	53,46	ng/ml
Androstenedione	**240**	**2912**	6	69	ng/dl
Testosterone	**74**	**152**	2,9	20	ng/dl
DHEAS	**21526,0**	**15087,4**	15	528	ng/ml

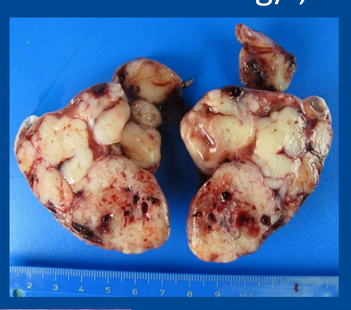
TMS-MS profile (Holterhus, Kulle, Kiel)

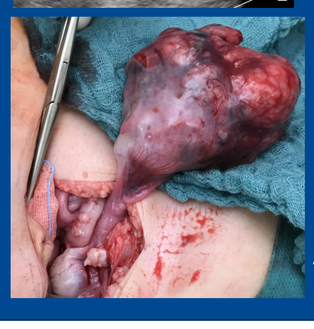
Further course complicated by JGCT:

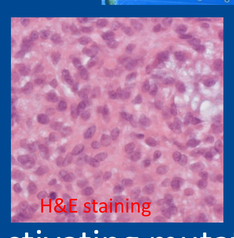
Acute abdominal pain at the age of four month, removal of ruptured tumor which proved to be a **juvenile granulosa cell tumor of the left ovary (JGCT)** (Tumor: 70g, 7,4 x 5,9 x 4,2cm, cysts up to 0,5cm)

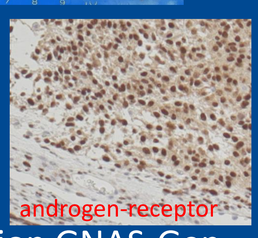
Lab.: Inhibin B 1222 ng/l, Estradiol 4741 ng/l, HCG <2,0 U/l, AFP 4,6 ng/ml











Activating mutation GNAS-Gen (c.602G>A; p.R201H) in tumor cells

Table 3

Marker	
PAS (Glykogen)	+
Panzytokeratin (AE1/AE3)	+
Vimentin, Inhibin	100% +
CD99, Calretinin	100% +
EMA, PLAP	-
AFP	-
CD117, OCT3l/4	-
CD30, Glypikan3	-
ß-HCG, SALL4	-
Estrogen-Rec	70% +
Progesteron-Rec	70% +
Androgen-Rec	100% +
Synaptophysin	-
Chromogranin	-
p53	10-20% +
MDM2	-
Ki67	20-30% +

Discussion:

JGCT is a rare tumor. Kalfa (2006) found 30% (n=30) to have an activating mutation of Gsα-subunit in tumor cells. In large series of MAS no patient with JGCT has been described (S. Lumbroso 2004). Only one single case with MAS and JGTC has been reported so far (BM. Al-Zoubi, Abstract Endo 2013). Therefore the activating mutation of Gsα-subunit cannot be the single factor of tumor development in JGCT.

In our case the JGCT developed in very short time (no tumor at previous ultra-sound 4 weeks before). It has to be assumed that the high estrogen levels due to the autonomous ovarian cysts (typical constellation for MAS) are one cause of JGTC growth as estrogens are well known growth factor for JGCT.

Additionally the very high androgen levels observed in our case during therapy with metyrapone might have been a relevant growth factor for the tumor, as androgen receptors were highly expressed in tumor cells (see table 3).

Conclusion:

Early manifestation of MAS due to activating GNAS mutation is accompanied by multiple organ involvement including autonomous ovarian cysts.

We present a case with hypercortisolism due to neonatal MAS and effective treatment with metyrapone, who developed juvenile granulosa cell tumor.

It has to be assumed, that the activating GNAS mutation, high estrogen levels and high androgen levels due to side effects of metyrapone caused rapid tumor development.

This has to be taken into account, when making the decision how to treat hypercortisolism in patients with neonatal MAS.

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