Sex differentiation, gonads and gynaecology or sex endocrinology 4

Virilization of a girl at puberty due to a unique translocation of an abnormal duplicated Y-chromosome to a deleted chromosome 9 including the DMRT1 gene

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Case report

- 11.5-year-old girl referred because of progressive cliteromegaly since 6 months
- *Physical exam:*
  - normal height (P10), overweight (BMI P90)
  - slight disproportions, no syndromic features
  - Pubertal stage: P5, B1-2, A1-2, rich bodily hair.
  - External genitalia with a marked cliteromegaly (Fig. 1)
  - no gonads palpable
- *Imaging:*
  - Bone age: concordant to chronological age
  - Ultrasound:
    - normal adrenals and gonads
    - prepubertal uterus
    - no tumor found
  - MRI: normal adrenals and gonads
- *24h-urine-steroid profiling:*
  - high excretion of androgen metabolites
  - exclusion of any form of late-onset CAH
- *Chromosome analysis:*
  - Karyotype 45,X (Fig. 2)

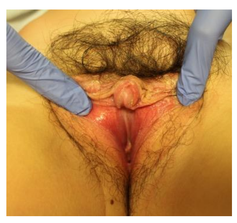

Fig. 1: Cliteromegaly of 3.5 x 1.5cm in size; otherwise normal looking female

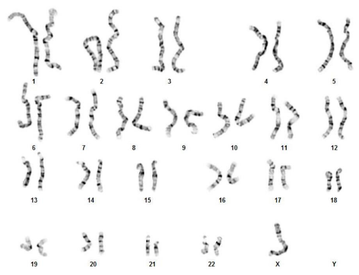

Fig. 2: Karyogram revealed karyotype 45X,0

- *Laboratory studies:*

	Age (years)	Events	ACTH (ng/L)	Cortisol (nmol/L)	DHEA (nmol/L)	DHEA-S (µmol/L)	Androstenedione (nmol/L)	fTestosterone (pmol/L)	11-Desoxycortisol (nmol/L)	17-alpha Progesterone (nmol/L)	LH (U/L)	FSH (U/L)	Estradiol (pmol/L)
		Reference	Ref. 7,2 - 63,6	(6-10 a.m.) (133-537) (4-8 p.m.) (68-327)	Ref. 3,9 - 20	Ref. 0,92 -7,6	Ref. < 8,4	Ref. 1.06 - 4.88	Ref. < 12	Ref. < 6	Ref. < 11.9	Ref. 2.1 - 11.1	Ref. < 84
At first presentation	11 5/12	Basal			3.8	1.32	<1.05	**23.3**	7.9	1.9	**12.5**	**37.5**	< 20
	11 5/12	ACTH- Test: basal/stimulated	2.1/-	227/ 680	4.0 / 6.8	1.02 /-	<1.05 / 1.12	14.8 / 12.5	/ 18.0	2.10/6.9	13.1/-	/39.4	<20
	11 5/12	Dexamethasone-suppressiontest	1.5	26	3.2	0.85	<1.05	12.6	2.5	1.7	15.3	42	<20
post -op day 1	11 7/12	Basal	<1.5	20	2.8	0.83		0.75			**19.6**	**44.1**	<20
late post - op (before estrogene E2 supplementation)	11 10/12		2.3	167	3.3	1.04	<1.05	2.34	5.3	0.7	**26**	**79.6**	<20

Table 1: laboratory studies at first presentation showed a significant androgen excess. LH and FSH were both markedly elevated (FSH>>LH), E2 undetectable. ACTH stimulation test showed normal reactivity of adrenal steroids and dexamethasone test suppressed normally. After laparoscopy and removal of the gonads androgen values noticeably dropped. (Data late post-operative under estrogene supplementation not shown here)

Objectives:

1. **How to explain androgen excess at puberty in a 45,X girl?**
2. **Where is the Y-material hidden?**
3. **What to do with a suspected androgen secreting gonad in 45,X**?

Material and Methods

- Expanded genetic exams in search of a hidden Y-chromosome including cytogenetic SRY-FISH analysis and Array-CGH
- Exploration of the gonads by laparoscopic and histopathological investigations

Results

1) Genetic analysis

- *FISH-Analysis* confirmed the presence of SRY-gene and showed a suspicious hybridization pattern (Fig. 2a & 2b)
- *Array-CGH-Analysis* revealed a terminal heterozygous deletion of 9p, monosomy of X and a terminal duplication of Yp

→ **45,X.ish der(9)t(Y;9)(SRY+) plus a terminal heterozygote deletion 9p24.3-p23**

- Resulting in a partial monosomy 9p including 49 genes, e.g. the sex gene *DMRT1* explaining a **complete sex reversal phenotype**

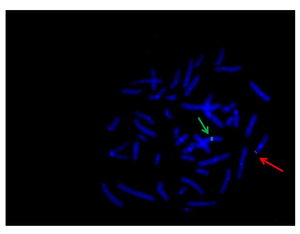

Fig. 2a: FISH-Analysis with LSI SRY/CEP X – probe shows unusual hybridization pattern. LSI-SRY-signal on chromosome 9pter

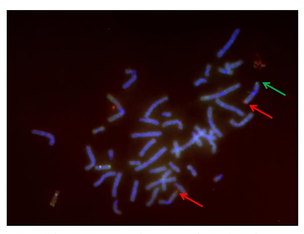

Fig. 2b: FISH-Analysis with SubTel-9p/9q- probe (9pter/9qter). No subtel 9p signal on derivative chromosome 9

2) Laparoscopic gonadectomy – macroscopic findings

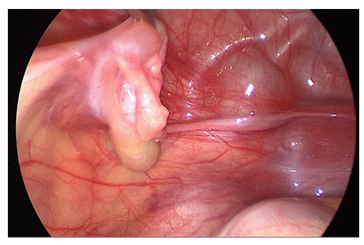

Fig. 3a: laparoscopic view of the dysgenetic gonad on the left

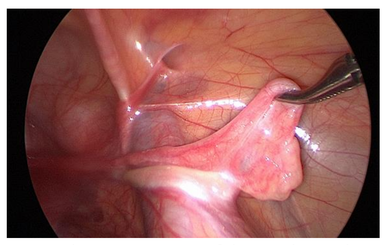

Fig. 4a: laparoscopic view of the streak gonad on the right

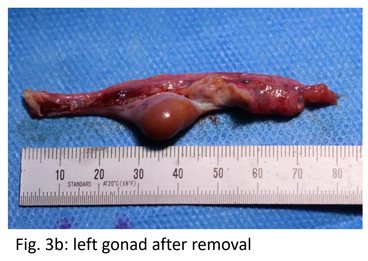

Fig. 3b: left gonad after removal

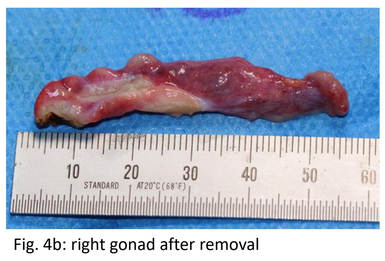

Fig. 4b: right gonad after removal

Complete sex reversal phenotype – mixed gonadal dysgenesis

3) Histopathologic results

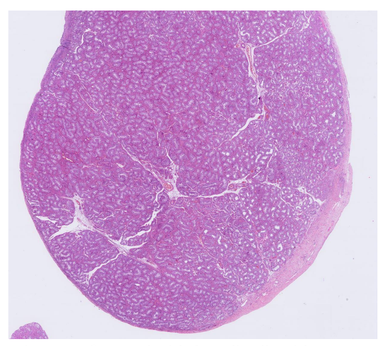

Fig. 5a: Left gonad with Sertoli cells with some granular changes but no germ cells and plenty of interstitially located Leydig cells

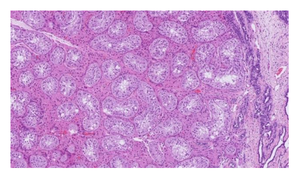

Fig. 5b

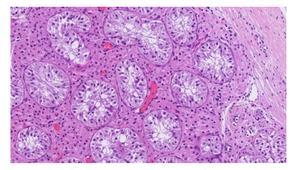

Fig. 5c

Fig. 5b&c: testicular tubules of the left gonad with Sertoli cells but no germ cells – flanked by rete testis (on the right)

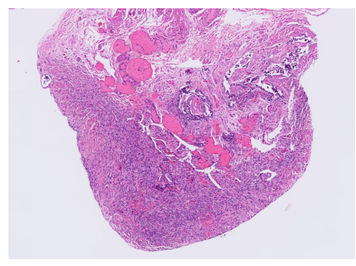

Fig. 6a: Streak gonad on the right with ovarial stroma, no germ cells

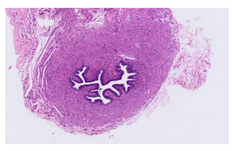

Fig. 6b: Tube with fimbrial funnel on the right

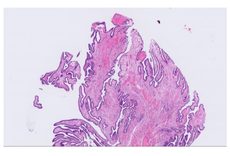

Fig. 6c: cross-section of the right tube

Conclusions

- Virilization at puberty in girls remains a challenge and can be more complex than routinely thought
- Several differential diagnosis must be considered including disorders of sex development (DSD) and tumors
- All efforts should be taken to find the underlying cause because ongoing virilization may result in irreversible bodily changes
- Repeat and expanded biochemical and genetic workup can be necessary to solve complex cases
- Multiple genetic hits can manifest with unique, unsuspected phenotypes as shown in the presented case report