A Novel Mutation of Anti-Mullerian Hormone Receptor Gene in a Male with Persistent Mullerian Duct Syndrome

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Background

Persistent Mullerian duct syndrome (PMDS) is a rare genetic disorder of internal male sexual development defined as a lack of regression of Mullerian derivatives in an 46XY male with normally virilized external genitalia and unilateral or bilateral cryptorchidism.

This condition is frequently diagnosed incidentally, during surgical repair of inguinal hernia or cryptorchidism.

Approximately 85% of the cases are caused by mutations of the anti-Mullerian Hormone (*AMH*) or its receptor (*AMHR-II*) genes, transmitted in an autosomal recessive pattern. About 38 mutation of the *AMHR-II* gene and 53 mutations of the *AMH* gene have been reported.

Serum AMH levels are used to distinguish between *AMH* and *AMHR* gene mutations. The levels are commonly low or undetectable in *AMH* mutations, while normal or high in the *AMHR-II* mutations.

Case presentation

A 3-months-old healthy male infant, first child of first-degree relative's parents was referred to the clinic for evaluation of cryptorchidism.

On examination, he had bilateral undescended testes with normal penile length without hypospadias and a mild hypoplastic scrotum.

At 3 months of age, he underwent elective inguinal hernia repair. During the surgery, fallopian ducts, uterus and two gonads in ovarian position were found (Figure1). At this point, since the diagnosis of his condition was unclear, the decision was to leave the Mullerian structures and the gonads in the peritoneal cavity without further surgical intervention.

Following the molecular diagnosis in our case and after discussion with the family of the most appropriate surgical approach in his case, bilateral orchiopexy and partial Mullerian remnant resection were performed.

Excision of the uterus, bilateral dissection and preservation of both vas deferens and blood supply to each testis were accomplished.

Both fallopian tubes were closely attached to the gonadal arteries.

The blood supply was preserved and bilateral orchiopexy to the scrotum without tension was undertaken.

At his last visit, aged 2.9 years, he was growing well (height 96 cm (+1 SD) and his weight 13.1 kg (-0.43 SD).

He had normal psychomotor development and on examination, the testis were palpable in the scrotum in 1.5 ml volume by Prader orchiometer.

TABLE 1: Hormonal results of the index case at 4 months age

Hormone	Value	Normal adult range
LH (IU/L)	5.9	1.5-9.3
FSH (IU/L)	1.19	1.4-18.1
E2 (pg/ml)	<11.8	
Testosterone (ng/ml)	0.97	0.75-4*
Cortisol (µg/dl)	10.1	5-25
COM-S (ng/ml)	3.7	<0.11-7.2
17OHP (ng/ml)	2.2	0.6-3.42
Prolactin (ng/ml)	16.83	2.1-17.7
Progesterone (ng/ml)	0.2	<0.2-1.2
DHEAS (µg/dl)	<15	80-560
TSH (µIU/ml)	7.69	0.4-4.2
FT_4 (pmol/L)	17.73	10-20
FT_3 (pmol/L)	8.15	3.5-6.5
AMH (µg/l)	>22	14-466**

* Normal range for 0-5 months old males
** Normal range for <24 months old males

Evaluation

karyotype, 46, XY

Hormonal study, normal serum levels of gonadotropins and testosterone for his age (Table 1)

Abdominal ultrasound scan demonstrated uterus but no gonads

AMH serum levels, >22 µg/l, Consistent with *AMHR* gene mutation

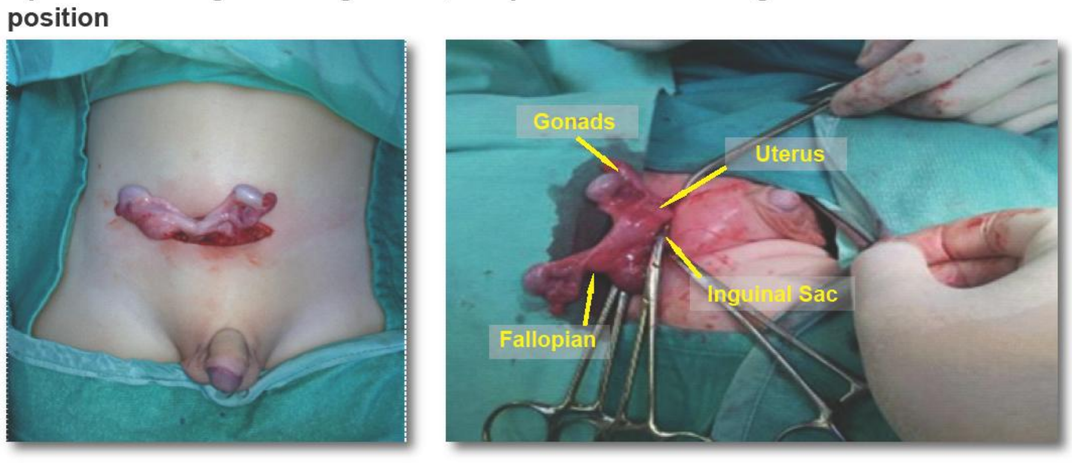
Serum AMH concentrations was measured by enzyme-linked immunosorbent assay (AMH Gen II, Beckman Coulter, Inc. A79765; Brea, CA, USA).

DNA analysis

Sequencing of the *AMHR-II* gene identified a novel homozygous missense mutation, C to T base substitution was found at position 928, near the middle of exon 7, changing codon CAG to TAG (stop codon) in *AMHR-II* gene. This mutation causes glutamine to be converted to terminator codon at position 928 (c.928C>T; p.Q310X) (Figure 2,3).

This mutation results in a lack of most of the intracellular serine/threonine kinase domain of the receptor. Both parents were heterozygous.

Fig. 1:
Operation findings showing uterus, fallopian tubes and two gonads in ovarian position



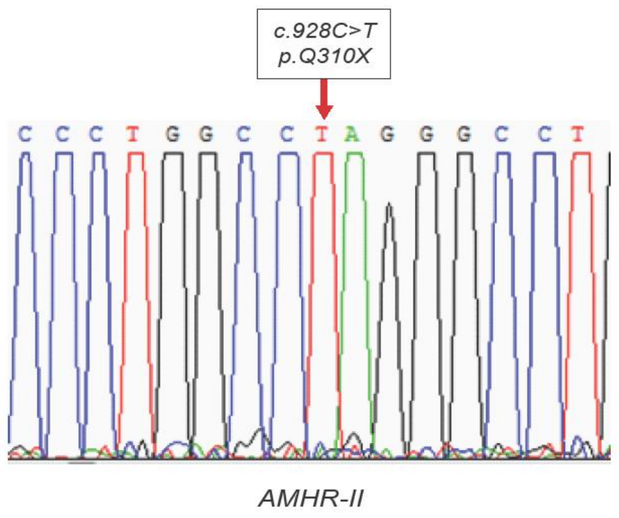


Fig. 2: Exon 7 of the *AMHR-II* gene showing the C to T base substitution mutation at position 928, near the middle of the exon 7, changing codon CAG to TAG (stop codon).

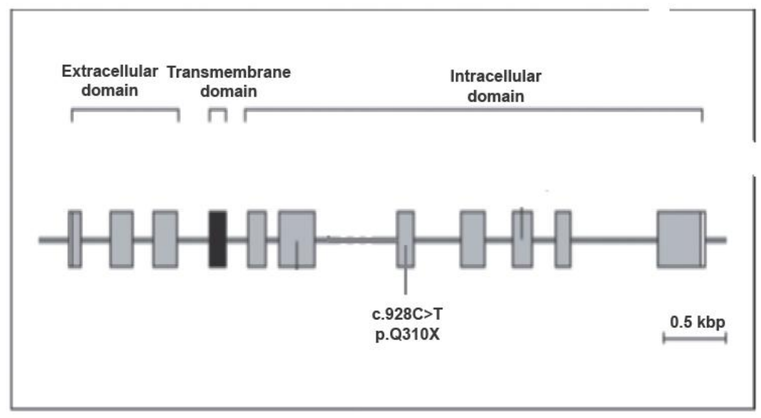


Fig 3: The *AMHR-II* gene showing the mutation in the middle of exon 7

Discussion

There is no consensus regarding the surgical approach in patients with PMDS.

Reports of Mullerian remnants malignancy and the known risk of testicular cancer in undescended testes encourage removal of the Mullerian remnants and bilateral orchiopexy. On the other hand, removal of the Mullerian structures has high risk of impair testicular and vas deferens blood supply, potentially causing infertility and impair testicular function.

Conclusions

AMH serum levels can distinguish between *AMH* and *AMHR* gene mutations in patients presented with PMDS, and may be followed by molecular sequencing of either gene

The current report emphasize the clinical dilemma in the surgical approach in these patients

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Sex Differentiation

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