DESCRIPTION OF A NEW VARIANT IN THE MAMLD1 GENE IN AN INFANT WITH MICROPHALLUS AND HYPOSPADIAS

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Introduction

The MAMLD1 gene is expressed in fetal and adult testes. It contributes to the development and formation of the male external genitalia in late stages of fetal organogenesis (week 8-12) and to testosterone biosynthesis. The pathogenic genetic variants of this gene determine a significant reduction in plasma testosterone concentrations, although they are not undetectable. Its most common phenotypic manifestation is hypospadias, also described in patients with microphallus with or without cryptorchidism.

Patient description

First visit

- 40 weeks gestation newborn with a microphallus of 1.5cm in length.

Physical exam

- Microphallus of 1.5cm in length (nv:3.5cm ± 0.4) and terminal hypospadias with 3ml testes located in the scrotal bag. Normal anthropometry.

Blood test

- Normal thyroid and adrenal hormone profile.
- Karyotype 46, XY.
- Normal hypothalamic-pituitary hormones studies.

			HCG 1000UI/d (6 doses)	
	6 days of live	**2 month**	**4 month(pre-test)**	**4 month3 weeks (post-test)**
Lenght	1.5cm	2cm	3cm	3cm
LH (nv: 0.40-10.1U/l 2-60 days)	4.4 U/L	4.8 U/L	< 0.12 U/L	< 0.12 U/L
FSH (nv: 0.6-7U/l 2-60 days)	3.8 U/L	3.0 U/L	1.12U/L	1.06 U/L
Testosterona (nv nn 300ng/dl)	**69 ng/dl**	**49 ng/dl**	**219.54 ng/dl**	**111.1ng/dl**
DHT (nv: 0.25-0.99ng/ml)		**0.1 ng/ml**	**0.07 ng/ml**	**0.05 ng/ml**
AMH (nv: 97.9 ± 34.4ng/ml)		77,2 ng/ml		
Inhibina B (nv: 209-321 pg/ml)		192 pg/ml		

Radiology

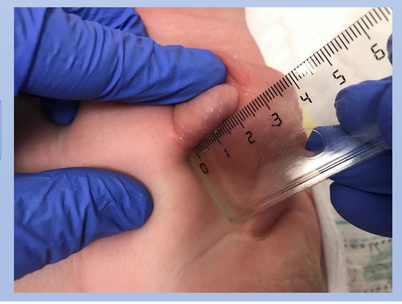
- Normal hypothalamic-pituitary magnetic resonance and testicular ultrasound with homogeneous echostructure and normal size testicles.

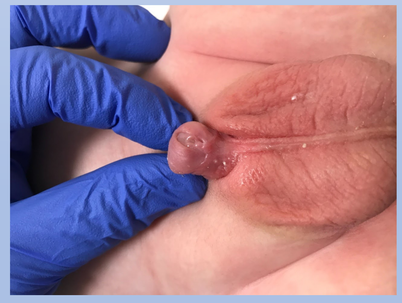
Genetics

- The DSD massive gene sequencing panel identifies a hemizygosity pathogenic variant in the MAMLD1 gene (c.1738C>T:p.Gln580Ter)in exon3).

Treatment

- Treatment with intramuscular testosterone 50mg every 3 weeks (2 doses) was started, showing a favourable response to treatment with an increase in penis length to 3.5cm.





Conclusions

- Our patient presents a pathogenic variant in MAMDL1 not previously described in the literature that predicts "in silico" a truncated protein that could justify his genital phenotype.
- The existence of low testosterone concentrations during the infant's minipuberty stage and the absence of a significant increase in plasma concentrations of testosterone and DHT in the hCG test highlights the potential role of this gene in the biosynthesis of testosterone during the fetal stage and minipuberty of the infant.
- This case would be the first time that a decrease in DHT has been described in a patient with an abnormal MAMLD1.
- M testosterone treatment is effective in these patients.

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