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

Cristina Aguilar Riera1, Dellanira Pamela Tutaya Egusquiza2, Gennaro Canestrino3, Paula Fernández4, Núria Camats5, Maria Clemente6, Diego Yeste6

1 Pediatric Service. Germans Trias I Pujol University Hospital2 Pediatric Service. Vall Hebron University Hospital3 Pediatric Endocrinology Service. Pediatric Service. Sant Joan de Déu Manresa Hospital4 Laboratory of Clinical and Molecular Genetics. Vall Hebron University Hospital5 Research Group Creixement I Desenvolupament. Vall d’Hebron Research Institute (VHIR). Vall Hebron University Hospital6 Section of Pediatric Endocrinology. Vall Hebron University Hospital.

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 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

- 40 weeks gestation newborn with a microphallus of 1.5cm in length.
- Microphallus of 1.5cm in length (rv:3.5cm ± 0.4) and terminal hypospadias with 3ml testes located in the scrotal bag. Normal anthropology.
- Normal thyroid and adrenal hormone profile.
- Karyotype 46, XY.
- Normal hypothalamic-pituitary hormones studies.
- The DSD massive gene sequencing panel identifies a hemizygous pathogenic variant in the MAMLD1 gene (c.1738C>T:p.Gln580Ter in exon3).
- 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 MAMLD1 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.