

Primary amenorrhea revealing Leydig cell hypoplasia

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Introduction :

Leydig cell hypoplasia (LCH) or agenesis, is an autosomal recessive condition and a well-defined form of 46,XY disorder of sex development (DSD) resulting from inadequate foetal testicular Leydig cell differentiation.

Inactivating mutations in the luteinizing hormone/chorionic gonadotropin receptor (LHCGR) gene account for the underlying LCH pathogenicity.

Case report :

We studied a 15-year-old female who presented at the Department of Endocrinology for primary amenorrhea. The patient was born at full term after an uncomplicated gestation of healthy consanguineous parents. A similar history with a female cousin was reported. Physical examination showed infantile breast development and absence of pubic hair growth. She had female external genitalia appearance with the external opening of urethra and short hypoplastic-two-centimetre-length vagina under a hypertrophic clitoris. Hormonal assessment showed plasma testosterone level at 0,38 ng/ml, which did not change after administration of human chorionic gonadotropin.

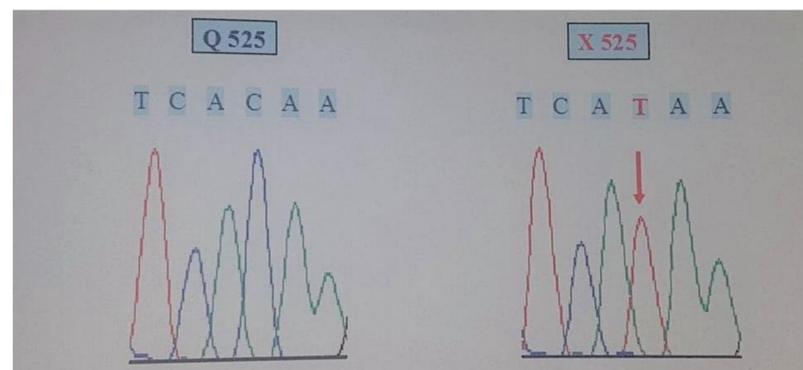
Luteinizing hormone (LH) plasma level was elevated at 60mUI/ml and was hyper-responsive after stimulation test with Luteinizing hormone-releasing hormone (LHRH). Estradiol was significantly low (<9 pg/ml) and serum FSH level was 6,4 mU/ml in the reference range.

Pelvic ultrasound showed two testes in inguinal regions, but no Müllerian structures.

Genetic analysis revealed that the karyotype was 46,XY and a homozygote nonsense mutation of LHCGR was confirmed, responsible of total resistance to LH hormone. It is a novel nonsense mutation of the second extracellular domain Q525X.

The same mutation was found heterozygous after genetic analysis of the parents DNA.

Our patient underwent a bilateral gonadectomy and a hormonal replacement with estrogen was started. At histology analysis no Leydig cells were seen.



LH receptor gene sequencing : controle (left) and our patient (right)

Discussion :

Leydig cell hypoplasia (LCH) or agenesis, is an autosomal recessive condition and a well-defined form of 46,XY disorder of sex development (DSD). Low testosterone and as a result dihydrotestosterone production results in impairment of the development of male external genitalia with variable phenotypes.

Type I LCH is the severe form of LCH caused by LHCGR mutations which results in a completely unresponsive LHCGR to hCG and LH, resulting in female external phenotype with a blind-ending vagina, lack of breast development, and primary amenorrhea in 46,XY subjects which was illustrated in our case.

47 inactivating mutations were identified, including missense mutations, nonsense mutations, insertions, and deletions. Genetic analyzing in our case isolated a novel nonsense mutation of the second extracellular domain Q525X.

We conclude that this case of female DSD was due to a Leydig-cell agenesis. 46,XY patients who are usually raised as female social gender may manifest ambiguous genitalia with elevated LH and decreased testosterone. Hormone tests are powerful tools and gene testing is helpful to establish the diagnosis.

References

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