CASE REPORT

Leydig cell hypoplasia type 1 diagnosed in early childhood with inactivating mutation in LHCGR gene

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Abstract

Leydig cell aplasia/hypoplasia is an autosomal recessive condition. In its complete form, these patients are 46XY but are cryptorchid and phenotypically female. Most cases reported in literature presented with in adolescence with pubertal delay. We reported a case with a predefined mutation in the LHCGR gene, presenting with swelling in the inguinal region and therefore diagnosed in early childhood. We wanted to emphasize the necessity of keeping Leydig cell hypoplasia in mind in the differential diagnosis of sexual development disorders in early childhood.

INTRODUCTION

Leydig cell hypoplasia (LCH) is an autosomal recessive disorder in individuals with a 46,XY karyotype, which is characterized by a predominantly female phenotype, a blind-ending vagina, absence of breast development, primary amenorrhea and the presence of testicular structures. It is caused by mutations in the luteinizing hormone/chorionic gonadotropin receptor gene (LHCGR), which impair either LH/CG binding or signal transduction [1]. We report a case with an inactivating mutation in the patient’s LHCGR gene that was previously described in another patient with LH receptor resistance [2].

CASE REPORT

The patient, who was the child of consanguineous marriage, was born a phenotypic female and grew up as a girl. When she was 2.5 years old, her family noticed swelling in the inguinal area. At first evaluation, the ovotestis compatible image was seen on the ultrasound. The patient was then referred to our pediatric endocrinology clinic for further evaluation of sex development disorder. Her past medical history was uneventful with no significant family history. On physical examination, her growth parameters were normal for her age. She was in good general condition and had no dysmorphic features. She had female external genitalia with the normal clitoris, separate urethral and vaginal openings (There were double holes.) There was no posterior labial fusion. Gonads were palpable bilaterally in the inguinal regions.

Uterus and other mullerian structures were not observed on abdominal ultrasound. Ovotesticular compatible images were detected; they were 15 × 8.7 × 24-mm size in the right inguinal region and 14 × 8 × 22-mm size in the distal left inguinal canal. Laboratory examination revealed normal levels of thyroid function tests, serum prolactin, serum cortisol, serum androstenedione (AS), serum 17 OH progesterone (17OH P) and serum dehydroepiandrosterone (DHEA-S). The levels of serum-follicle-stimulating hormone (FSH): 6.1 IU/L (N: 1.4-4.5), serum luteinizing hormone (LH): 12.53 IU/L (N: 0.1-6) serum testosterone (T): 13.16 ng/dl (N: 14-76) and serum anti-Mullerian hormone (AMH): > 23 ng/ml (N: 1.43-11.6) were monitored [3].

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phenotype revealed a 46,XY male karyotype in all metaphases. The fluorescence in situ hybridization revealed the presence of the SRY gene on the Y chromosome.

After the initial hormonal profile of the patient was recorded, the hCG stimulation test was performed. About, 1500 units/day hCG was administered intramuscularly for three consecutive days. There was no significant change in the serum testosterone concentration (12 ng/dl) compared to baseline values. Dihydrotestosterone (DHT) level was not evaluated because there was no increase in testosterone level with the hCG stimulation test. In contrast to testosterone biosynthetic defects, no precursor steroids of our patient were elevated. Because of poor response to the hCG stimulation test, high FSH, LH and AMH, low testosterone levels, ovotesticular appearance on ultrasound, 46,XY karyotype, the patient was directed to the molecular genetics department to investigate possible LHCGR mutations/polymorphisms.

The homozygous p.R479* (c1435C>T) mutation in the LHCGR gene, which was previously reported in the literature, was observed in individuals with 46,XY gender developmental disorders. Even though it rarely presents in early childhood, it should be kept in mind as the differential diagnosis of sexual development disorders.

DISCUSSIONS

Inactivating mutations of human LHCGR have been described in 46, XY individuals with a rare form of disorder of sex development, termed Leydig cell hypoplasia. These inactivating mutations in the LHCGR prevent LH and hCG signal transduction and thus testosterone production both pre- and postnatally in genetic males [4]. In contrast to activating LHCGR mutations, which result in gonadotropin-independent male-limited precocious puberty, no phenotype has been observed in heterozygous patients with loss-of-function mutations of the LHCGR, underlining the recessive character of these mutations [5]. Inactivating mutations in the LHCGR are rare, and there is an apparent genotype phenotype correlation dependent upon the degree of LHCGR inactivation. Mutations involving the LHCGR gene associated with a female phenotype are rare. A few mutations have been described in the LH receptor associated with female or ambiguous external genitalia [2]. Our patient was diagnosed in early childhood period, unlike patients with LHCGR mutation, who are usually diagnosed with primary amenorrhea.

In normal males, luteinizing hormone (LH) regulates the function of Leydig cells and hence, male sexual differentiation, pubertal androgenization, male sexual function and fertility. Abnormalities in the function of Leydig cells result in primary hypogonadism and varying degrees of disorders of sex development [6]. In normal women, LH stimulates the theca cells to produce androgen precursors for aromatization to estradiol by granulosa cells during the follicular phase of the menstrual cycle [7].

Leydig cell aplasia/hypoplasia is an autosomal recessive condition. The underlying abnormality in this disorder is a failure of Leydig cell differentiation secondary to an abnormal LHCGR. LH is elevated, testosterone (T) is markedly decreased and follicle-stimulating hormone (FSH) levels are unaffected. There is no T surge on hCG stimulation and studies of testicular-biopsy samples from some patients have revealed the absence of LH receptors [8]. Our patient with a typical male chromosomal pattern (46,XY) had female external genitalia, and there was no testosterone response to hCG stimulation.

In genetic males, mutations in LHCGR are associated with distinct degrees of impairment in pre- and postnatal testosterone secretion resulting in a phenotypic spectrum. In its complete form, these patients are 46,XY but are cryptorchid and phenotypically female. Wolffian structures are present due to the secretion of AMH by intact Sertoli cells. Patients with the severe form (type 1) of LH resistance have predominantly female external genitalia and absence of secondary sex differentiation at puberty. Patients with milder forms (type 2) have predominantly male external genitalia with micropenis and/or hypospadias or only infertility without ambiguity [4, 8]. In these patients, male external genitalia failed to develop in utero, but there is some development of pubic hair during and after puberty, most likely in response to normally increasing concentrations of adrenal androgens in this period [5].

Overall, the incidence of sex development disorders appear to be higher in countries, that allow endogamy. Similarly, in a study in the literature, consanguineous marriage was more commonly observed in individuals with 46,XY gender developmental disorders [9]. The parents of our patient were first degree cousins as reported in the literature.

The aim of this study is to raise awareness about Leydig cell hypoplasia. Even though it rarely presents in early childhood, it should be kept in mind as the differential diagnosis of sexual development disorders.

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None.

CONFLICT OF INTEREST

None declared.

FUNDING

None.

ETHICAL APPROVAL

There is no need for ethical approval for a case report according to the local ethical guidelines.

CONSENT

A written informed consent was taken from the patient’s parents.

GUARANTOR

None.

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