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Case Report

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5-α Reductase Deficiency in Two Siblings: A Case Report

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Abstract

A deficiency of 5-α reductase is a rare genetic disorder that affects 46,XY patients. The lack of enzyme causes inadequate differentiation of the gonads, leading to ambiguous genitalia or complete feminization of the external genitalia. Two sisters presented to their endocrinologist complaining of primary amenorrhea. Molecular studies revealed the SRD5A2 His231Arg gene mutation and karyotype showed 46,XY genotype. The diagnosis was supported by their high testosterone/dihydrotestosterone (DHT) ratio, response to the hCG stimulation test and their elevated sex hormone binding globulin (SHBG) levels. The siblings continued to identify as the female gender and were placed on oral premarin to develop secondary female sexual characteristics. In conclusion, any individual presenting with ambiguous genitalia, primary amenorrhea or virilization should be investigated for 5-α reductase deficiency by conducting a karyotype and full hormone profile

Keywords: Amenorrhea; Ambiguous; Genitalia; Androgen; Insensitivity; Differentiation; Testosterone; Dihydrotestosterone; 5-α reductase

Introduction

Human sexual development is a complex process that begins *in utero*. Depending on the individual's genotype, the bipotent gonads differentiate into ovaries or testes [1]. This differentiation is a result of not only the chromosomal constitution, but also the hormonal influences that manipulate the expression of sexual characteristics. Dihydrotestosterone (DHT) is a potent hormone that plays a crucial role in the development of male external genitalia [2]. Without DHT, one with a 46,XY karyotype may appear phenotypically female due to undervirilization [2, 3]. DHT is a derivative of testosterone; the enzyme 5-α reductase type 2 is responsible for its conversion [4]. Therefore, a lack of 5-α reductase type 2 could also lead to ambiguous genitalia and undervirilization [4]. Androgen receptors must be present and responsive to DHT and testosterone in order for external sexual characteristics to take effect. A defect in any of the previously mentioned enzymes or hormone receptors could lead to discordance between genotype and phenotype [5].

Androgen insensitivity is the most common disorder of sexual development with an incidence of 2:100,000 to 5:100,000 [6]. It is an X-linked recessive disorder in which there are mutations coding for the androgen receptor leading to partial androgen insensitivity, complete androgen insensitivity or mild androgen insensitivity [5]. Partial androgen insensitivity syndrome (PAIS) is just as common as complete androgen insensitivity syndrome (CAIS), if not more [6]. Since it is the most prevalent disorder of sexual development, a diagnosis of androgen insensitivity is often made for those presenting with ambiguous genitalia or pubertal virilization [4].

5-α reductase deficiency is an autosomal recessive disorder. Although frequencies for this deficiency are not established, the highest populations have been noted to be in Turkey, the Dominican Republic and New Guinea in regions of high consanguinity [7]. Diagnosis is usually made at birth with the infant presenting with ambiguous genitalia [4]. However, on occasion, the infant is completely undervirilized and diagnosis is not made until puberty when the individual presents with primary amenorrhea [8]. This case report will discuss two siblings that presented with primary amenorrhea. The siblings were both given a clinical diagnosis of androgen insensitivity; however, upon further investigation the siblings were found to have the SRD5A2 gene mutation, His231Arg, consistent with 5-α reductase deficiency.

Case Report

A 17-year-old woman (1P) presented with primary amenorrhea. On physical examination, 1P displayed tanner stage 2 breast development. The external genitalia was normal apart from mild clitoromegaly. The vagina was blind ending and measured 4 cm in length and 2 cm in width. Chromosomal analysis displayed a 46,XY genotype. A diagnosis of androgen insensitivity was assumed until molecular studies revealed the SRD5A2 His231Arg gene mutation, consistent with 5-α reductase deficiency. She underwent laparoscopy and bilateral inguinal gonadectomies. The patient's younger sister (2P) aged 14 came in with a similar presentation. Chromosomal and molecular analysis concluded a deficiency of 5-α reductase. An MRI revealed complete absence of internal genital organs for 1P and 2P.

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Testosterone levels were within normal range for males in tanner stage 2 development. 1P and 2P had testosterone levels of 0.85 and 0.80 nmol/L, respectively. Their DHT levels were very low. 1P had a level of 0.048 nmol/L and 2P had a level of 0.049 nmol/L. In order to support the diagnosis, an hCG stimulation test was performed. In both siblings, when hCG was administered, the testosterone levels increased and the DHT levels remained as they were. The testosterone/DHT ratio rose from 17.6 to 31.88 for 1P and rose from 16.2 to 32.08 for 2P.

Sex hormone binding globulin (SHBG) levels were much higher in comparison to tanner stage 2 males and females, reaching 263 and 259 nmol/L for 1P and 2P, respectively.

Discussion

Individuals with 5-α reductase deficiency are often born with ambiguous genitalia. At birth, these people are either diagnosed with the enzyme deficiency or misdiagnosed with androgen insensitivity syndrome [5]. However, certain genotypically male infants are born completely undervirilized and appear phenotypically female. In these situations, disorders of sexual differentiation are not diagnosed until puberty [3]. In the case discussed, the two sisters both presented to their endocrinologist with primary amenorrhea and were found to have the SRD5A2 gene mutation on chromosome 2, His231Arg. Despite this uncommon presentation, it is essential for clinicians to consider this deficiency when encountering either a 14-year-old female patient without secondary sexual characteristics who has yet to menstruate or a 16-year-old female with secondary sexual characteristics who has yet to experience menarche.

Over 19 mutated variants have been identified on the SRD5A2 gene [9]. Previous research suggests that individuals with 5-α reductase deficiency may either have a homozygous or heterozygous gene mutation. The His231Arg mutation has been reported both as a heterozygote and as homozygote [9]. Due to the lack of virilization during puberty, it is possible that this specific mutation is severe, yielding an extremely female phenotype. So much so that it may be comparable to complete androgen insensitivity syndrome CAIS [10]. Patients 1P and 2P did not display any signs of virilization bar mild clitoromegaly. It is common for these individuals to receive a working diagnosis of CAIS.

In this case report, the two siblings both had elevated levels of SHBG. DHT has been shown to regulate plasma SHBG. Therefore, a lack of DHT would allow for elevated SHBG levels [11]. Higher levels of circulation SHBG decrease the amount of free circulating sex hormones. Testosterone has a high affinity for SHBG. Therefore, the elevated SHBG levels and decreased free testosterone levels account for the lack of virilization exhibited by the patients at puberty [11].

Despite elevated SHBG levels, testosterone levels were normal, and the testosterone/DHT ratio was increased. In other cases of 5-α reductase deficiency, the testosterone/DHT ratio is also increased [1].

Both siblings chose to continue identifying as the female gender. They were placed on oral premarin to promote secondary sexual development. Vitamin D was prescribed in order to maintain bone density. Despite the discordance between genotype and phenotype, both individuals are physically healthy. Due to the lack of female internal organs, they are unable to have children of their own. The mental health of both women should be monitored since women living with 46,XY disorders of sexual development are more likely to develop depression and anxiety [11].

In summary, a deficiency of 5-α reductase is a genetic disorder that affects both newborn children and pubescent adolescents [4, 10]. Based on this case report, it is recommended that patients presenting with primary amenorrhea, ambiguous genitalia and evidence of virilization be investigated for 5-α reductase deficiency. A full workup includes a hormone profile (DHT, testosterone, SHBG levels, hCG stimulation test and a testosterone to DHT ratio), a karyotype and molecular analysis. In addition, due to the inheritance pattern and variability of the clinical picture, siblings of individuals with 5-α reductase deficiency should also undergo genital system examinations, chromosomal and molecular analysis.

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