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CASE REPORT

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5-Alpha reductase deficiency; an important cause of 46, XY DSD: Report of three cases within a family

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Key clinical message

5-Alpha reductase deficiency is an important cause of 46, XY disorder of sex development. Timely diagnosis and proper management by a multidisciplinary team can lead to a favorable outcome. Sex assignment should be deferred until puberty because spontaneous virilization occurs and the patient can engage in the decision-making process.

Abstract

5-Alpha reductase deficiency is a genetic disorder causing 46, XY disorder of sex development (DSD). Typical clinical feature is a male with ambiguous genitalia or undervirilization at birth. Here we report three cases of this disorder within a family.

KEYWORDS

5-Alpha reductase deficiency, dehydrotestosterone, disorder of sex development

1 | INTRODUCTION

5-Alpha reductase is an enzyme responsible for conversion of testosterone to dehydrotestosterone (DHT) in androgen target tissues. Deficiency of this enzyme results in intrauterine abnormal male sexual development and also during puberty.[1] This is a rare genetic condition with autosomal recessive inheritance.[2] Mutations in SRD5A2 causes this disorder. Affected males are born with undervirilization of the external genitalia or 46, XY disorder of sexual development (DSD). The Wolffian structures exist and are normally differentiated but the appearance of the external genitalia may range from normal female to undervirilized male at birth.[5] Children with this condition are usually raised as female and during puberty they develop some male sex characteristics like voice changes and increased muscle mass.[5]

Most cases of this condition are reported from countries with high rates of consanguine marriages like: Papua new Guinea, Dominican Republic, Turkey, and Lebanon.[3] The prevalence of this condition in the general population is not known[4] and we do not have data about its prevalence in Iran.

Here we report three cases of 5-Alpha reductase deficiency in a family in Iran. Written informed consent was obtained from the patients or their guardian to publish this report.

2 | CASE REPORT

A 6-month-old baby was referred to the endocrine clinic of Imam Reza hospital, Mashhad, Iran, because of clitoromegaly and palpation of a mass in the inguinal area. The mother had noticed this mass recently. Because female external genitalia was present at birth the patient was assigned as female. The patient was the second baby of a consanguine marriage (parents were cousins) and the first child was a normal 6-year-old boy.

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On physical examination, a mass was palpated in the right inguinal area and a blind vaginal pouch was detected.

Ultrasound of the abdomen and pelvis showed that there was no ovaries and uterus. Testis was detected in the left side and also in the right inguinal canal. Karyotype revealed 46, XY Pattern. Biochemical analysis was as follows: Serum testosterone: 15 ng/dL, DHT: 21 pg/mL, FSH: 2.8 mIu/mL, LH: 2.4 ng/dL.

Whole exome sequencing revealed homozygote mutation of the SRD5A2 gene and a diagnosis of 5-Alpha reductase deficiency *was confirmed*. After psychological counseling and because gender identity was not still established, the patient underwent a surgery and hypospadias was corrected, orchiopexy was performed, and an acceptable male external genitalia was made for the patient (Figure 1).

On follow-up he is a normal boy with normal physical growth and normal male gender identity and behavior.

The second case is this patient's aunt who is 35 years old. Third child of a consanguine marriage. She was assigned as female because of the appearance of the external genitalia and she went undiagnosed until puberty when she developed clitoromegaly and increased muscle mass and voice change. Breast development and menarche did not appear. She had been investigated and 5-Alpha reductase deficiency confirmed. Patient was counseled but because she was brought up as female, a decision to perform orchidectomy was made and correction surgery of the external genitals was performed. She is now a female with strong physics and acts in contact sports professionally.

The third case of this family is the first patient's mother's cousin (see the pedigree- Figure 2). He is now 27 years old. He was also assigned as female but with the onset of puberty and appearance of clitromegaly and voice changes he was investigated and a diagnosis of 5-Alpha reductase deficiency was made. Psychological counseling was performed and he was sex changed to male. He is now a normal male with normal male behaviors. He has married and has a normal child.

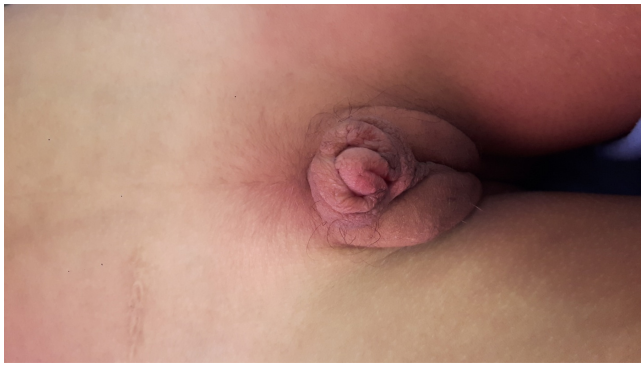

FIGURE 1 Patient's external genital after reconstruction surgery.

3 | DISCUSSION

In this report we presented three patients with 5-Alpha reductase deficiency who were relatives. Their clinical characteristics were reported and were those typically presented in the literature.

Infants whose external genitalia are not typically male or female or their genital appearance is not compatible with their chromosomal sex are considered to have disorder of sex development or DSD.[1] XY DSD occurs due to insufficient androgen action. 5-Alpha reductase deficiency is one of the causes of XY DSD. This is a condition with autosomal recessive inheritance.[2] 5-Alpha reductase is the enzyme responsible for the conversion of testosterone to dehydrotestosterone (DHT).

Typical clinical feature of this disorder is a 46, XY male with female appearance of the external genitalia at birth. However, it may present as varying degrees of undervirilization in a male infant..[5,6] The internal genital structures are male and mullerian structures are absent because anti mullerian hormones do act normally.[7] Most children with this condition are diagnosed at birth due to the atypical appearance of their external genitalia but in cases that go underdiagnosed because of the typical female appearance of their genitalia, the diagnosis is always made at puberty while the secondary male sexual characteristics like increased muscle mass and voice changes ensue.[8] This was true for our second and third case. Our first reported case was also with typical female genitalia but was diagnosed sooner due to the presence of inguinal hernia and palpation of the testes.

Biochemical findings that support the diagnosis of 5-Alpha reductase deficiency are that of a normal serum testosterone value and increased ratio of serum testosterone to DHT.[9] Definitive diagnosis is made via DNA mutation analysis.[10,11] This was performed in our first patient and mutation of SRD5A2 gene was detected and final diagnosis confirmed.

Treatment of children with 5-Alpha reductase deficiency depends on many factors. The most important factor is the patient's phenotype and gender assignment at the time of diagnosis.[12]

Multidisciplinary team with good expertise in disorders of sex development is needed for the best management of these patients.[13] Issues like sex assignment and psychosocial condition of the patients and their families must all be considered. Patients who are diagnosed in the newborn period should be raised as male, because with the onset of puberty virilization will occure.[14] For

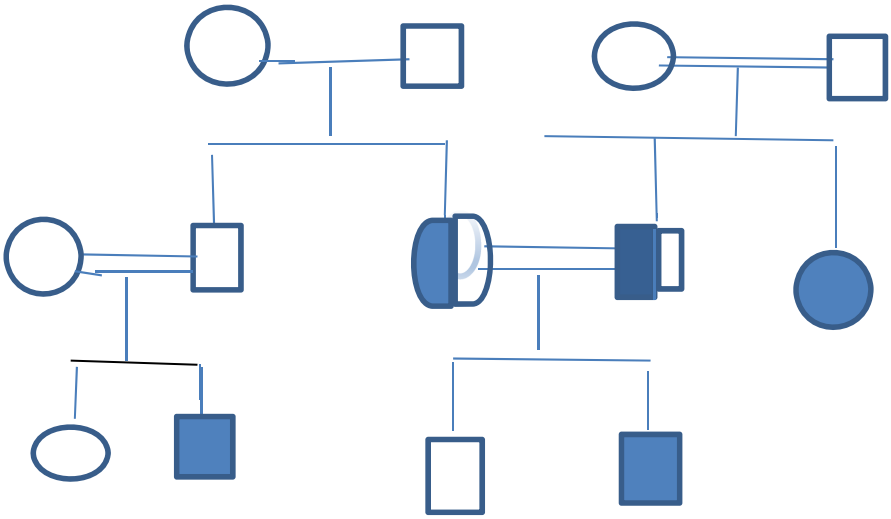

FIGURE 2 Pedigree showing patients relationships.

children who are diagnosed later the condition is complex and the choice of sex assignment must be made in consultation with the child and his family.[13] If the decision is made that the child be raised as female then gonadectomy must be performed to minimize the risk of tumors in the testis and also prevent virilization[15]and the external genitalia should be corrected surgically. Our second patient was raised as female and diagnosis was made after the onset of puberty and she decided to remain as a female so gonadectomy was performed for this case. Estrogen therapy for the induction of breast development and also prevention of osteoporosis is indicated in these cases.

For subjects who are raised as male or have changed their sex into male, supplemental androgen therapy is needed to improve virilization and phallic growth.[16]

4 | CONCLUSION

5-Alpha reductase deficiency should be considered in the differential diagnosis of children with 46, XY DSD and treatment of these patients is best performed in centers with multidisciplinary teams with expertise in the management of DSDs. With proper management, both scenarios regarding sexual identity can have splendid outcome as seen in our report.

AUTHOR CONTRIBUTIONS

Samaneh Noroozi asl: Conceptualization; supervision; writing – review and editing. **reza ibrahimi:** Investigation; software; writing – review and editing. **sepideh bagheri:** Conceptualization; investigation; writing – original draft; writing – review and editing. **mojtaba lotfi:** Investigation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

None.

CONSENT

Written informed consent was obtained from patients or their guardian to publish this report.

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