

OVERLOOK THE ANDROGEN INSENSITIVITY SYNDROME WITH A FAMILIAL CASE STUDY

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ABSTRACT :To objective of this study was to present androgen insensitivity syndrome is seldom seen, in a family with three affected individuals.

A 16-year-old, a 17-year-old, and a 18-year-old phenotypic female three individuals with primary amenorrhea were evaluated through a diagnostic protocol that included clinical, cytogenetic, and hormonal examinations. After the patients were diagnosed as androgen insensitivity syndrome, they were operated on for gonadectomy and vaginoplasty with pudental thigh flap and postoperative long-term exogenous estrogen replacement therapy was started.

The patients have successfully been followed with exogenous estrogen replacement therapy for six years, which gives them comfortable social and psychosexual life as women in accordance with their desire.

[Key Words: Androgen insensitivity syndrome, familial case.]

INTRODUCTION

Androgen insensitivity syndrome (AIS), also called testicular feminization syndrome, is a form of X-linked male pseudohermaphroditism. The disease is the result of an end-organ resistance to androgens caused by an abnormality in androgen receptors. There is a postreceptor abnormality (1). The androgen receptor (AR) is a ligand-dependent transcription factor. It takes part in various biological processes such as sex differentiation, sexual maturation and spermatogenesis (2). The androgen receptor gene locus has been mapped to the q_{11,12} region of the human X chromosome (3,4). There are some mutations of this gene, especially clusters in exon 5 and exon 7 (5). These mutations cause phenotypic abnormalities of male sexual development (6). The phenotypes vary from women with female external genitalia through

patients with genital ambiguity to men with normal male genitalia but infertile (2). The incidence of this syndrome has been reported in 1:20400 new borns (7). The karyotype is 46,XY. But, cases with chromosomal mosaicism have also been reported (8). Primary amenorrhea is the most frequent complaint in postpubertal patients. However, inguinal hernia may be cause for consultation in prepubertal patients with AIS (7). There are two types of AIS: complete and incomplete. The individuals with the incomplete AIS form differ from the complete AIS form by having enlarged phallus at birth and a less complete feminization at puberty (9,10). Gonadectomy is advisable at puberty to avoid the increased risk of neoplasia (11).

Here we report a case; testicular feminization syndrome that is seldom seen was detected in three sisters, they were consecutively treated with surgical and

hormonal therapies, which gave the patients comfortable psychosexual and social life as women, so these patients were evaluated for a case report.

Case Report: A 16-year-old, a 17-year-old, and a 18-year-old phenotypic female three sisters applied to gynecology clinic for primary amenorrhea in 1993. They were evaluated through a diagnostic protocol that included clinical, hormonal, and cytogenetic examinations. Their heights were 172 cm, 168 cm, and 165 cm and their weights were 50 kg, 54 kg, and 56 kg respectively. All of them had scant pubic and axillary hair, cliteromegaly, and vagina ends as a blind pouch. They had unambiguous female external genitalia. They had absence of Müllerian duct derivatives (no

uterus, no fallopian tubes), no ovaries. All sisters had bilateral palpable testes in inguinal canal. Each one's breast score was 2 in accordance with Tanner classification (12). They had no any other anomalies. Initial basal follicle-stimulating hormone (FSH) (normal range is 1.4-18.11mIU/mL for male, Chiron/Diagnostics, Fernwald, Germany), luteinizing hormone (LH) (normal range is 1.5-9.3 mIU/mL for male, Chiron/Diagnostics, Fernwald, Germany), estradiol (E2) (normal range is 21-76 pg/mL for male, Chiron/Diagnostics, Fernwald, Germany), and total testosterone (TST) (normal range is 241-827ng/dL for male, Chiron/Diagnostics, Fernwald, Germany) levels of three sisters supported the diagnosis of testicular feminization syndrome (Table 1).

Table 1. Karyotypes and Initial Hormonal Data of Three Individuals with Androgen Insensitivity Syndrome

Case No	Age, y	Karyotype	FSH* mIU/mL	LH* mIU/mL	Estradiol pg/mL	Testosterone ng/dL
1	16	46,XY	60.6	83.7	28.7	438.2
2	17	46,XY	62.8	112.4	37.5	390.87
3	18	46,XY	64.9	146.9	42.6	415.8

* FSH : follicle-stimulating hormone, LH : Luteinizing hormone

Karyotypes of all sisters were 46,XY. Three sisters with testicular feminization syndrome were operated on for gonadectomy and vaginoplasty with pudental thigh flap in 1994. No complications occurred during and after operations. Postoperative long-term exogenous estrogen replacement therapy was initiated for each one. Every sisters has taken estrogen 2.5 mg/d for 6 years. At last examination, each one's breast score was 3 in accordance with Tanner classification and their

pubic and axillary hair were scanty. After the treatment follicle-stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone (TST) levels of three sisters decreased, while estradiol (E2) levels of them increased (Table 2). These patients were treated in accordance with their phenotype as they desired. We believe that we have helped our patients for appropriate social and psychosexual lifestyle with these therapies

Table 2: Hormonal Data of Individuals After Gonadectomy and Exogenous Estrogen Replacement Therapy

Case No	Age, y	FSH* mIU/mL	LH* mIU/mL	Estradiol pg/mL	Testosterone ng/dL
1	22	4.6	4.36	159.65	53.9
2	23	4.2	5.37	144	40.68
3	24	5.48	6.94	157.99	42.64

* FSH : follicle-stimulating hormone, LH : Luteinizing hormone

DISCUSSION

Androgen insensitivity syndrome (AIS) is the result of an end-organ resistance to androgens. There are some mutations of the androgen receptor gene, which cause abnormal functions. Disorders of the androgen receptor (AR) function cause a wide spectrum of abnormalities of phenotypic male development, ranging from individuals with mild defects of virilization to those with complete female phenotypes. In this group, the gonadal sex is at variance with the genital sex. Male pseudohemaphroditism is seen (karyotype is 46,XY). Patients with AIS have testes may be either in the pelvis, or in the inguinal canal or in the labia majora, and absence of Müllerian duct derivatives, no ovaries. There is a spectrum of deficiencies of masculinization in this syndrome.

We presented here three sisters with androgen insensitivity syndrome that is rarely seen. They had primary amenorrhea, scant pubic and axillary hair, cliteromegaly, palpable testes in inguinal canal, vaginal ends as a blind pouch, and no ovaries, no uterus, and no tubes. Karyotypes of three sisters were 46,XY and they were phenotypically females. Gonadectomy, because high incidence of developing gonadal malignancy (11), and vaginoplasty were done. After the surgical treatment, all sisters have taken hormonal therapy for six years. They had scant pubic and axillary hair as we expected and breast score of all them were 3 in accordance with Tanner classification at last examinations.

Hormonal findings in three sisters presented here agree with those of previous reports on AIS. Before the treatment, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels of patients were higher than normal men, while total testosterone (TST) and estradiol (E2) levels of them were within the normal male range. The characteristic endocrine findings in AIS are the circulating level and production rate of testosterone by testes is the same as or higher than normal men and elevated levels of luteinizing hormone (10,13). These alterations

are due to an abnormality in the androgen receptor gene that causes end-organ resistance (10,14). Serum LH concentration is increased, presumably as a result of the resistance of hypothalamic pituitary system to androgen inhibition. The increase in estradiol levels might result from estrogen production in testis (15). AIS patients maintain the secretion of FSH by a combined action of estradiol and gonadal hormones such as inhibin (16). We suppose that estradiol levels were insufficient to regulate production rate and circulation levels of FSH in these cases, so there were increases in FSH levels of these cases before the treatment. Exogenous estrogen replacement therapy caused increase in estradiol levels as decrease in FSH and LH levels.

In conclusion, mutations in androgen receptor (AR) gene, mapped to human X chromosome, have been reported in some previous studies. Although we were not able to study mutations of these patients, we evaluated these patients to present as a case report, because three sisters with complete androgen insensitivity syndrome are rare cases.

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