Partial Androgen Insensitivity Syndrome: Prevalence Among Primary Amenorrheic Patients and an Analysis of Eight Cases

Parsiyel Androjen Duyarsızlık Sendromu: Primer Amenoreli Hastalardaki Prevalans ve Sekiz Olgunun İncelenmesi

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ABSTRACT Objective: To determine the prevalence of partial androgen insensitivity syndrome among primary amenorrheic patients and to report analysis of eight cases. **Material and Methods:** We retrospectively reviewed the records of adolescent patients with primary amenorrhea, in 2005, to determine the prevalence of patients having partial androgen insensitivity syndrome. And we also analysed the files of 8 patients; 7 of whose gonads were removed with the diagnosis of partial Androgen Insensitivity Syndrome (AIS) between the years 2003-2005. Their chief complaints, clinical and laboratory findings, findings at surgery, postoperative pathologic findings and treatment after gonadectomy were reviewed and discussed. **Results:** During the year 2005, 725 patients applied to adolescent gynecology unit with the complaint of menstrual irregularities. Thirty-nine of them (5.37%) had primary amenorrhea. Of these 39 patients 2 (5.12%) had 46 XY karyotype. One of them was testicular feminization (complete androgen insensitivity syndrome), and the other (2.56%) was pseudohermaphroditism (partial androgen insensitivity syndrome). Between 2003-2005, seven of 8 patients' gonads were removed. One patient was 10 years old, therefore gonadectomy was planned for her, after puberty. **Conclusions:** The prevalence of androgen insensitivity syndrome is usually given as the ratio among live births. We think that prevalence among primary amenorrheic patients will be more useful in clinical practice. Chromosome analysis should be done in every patient with primary amenorrhea having elevated gonadotropin levels. The usual treatment for partial androgen insensitivity syndrome is gonadectomy after puberty and hormone replacement therapy. However, counseling and pschological follow-up are essential components of the management protocol.

Key Words: Androgen-insensitivity syndrome; pseudohermaphroditism; puberty; hormone replacementtherapy

ÖZET Amaç: Primer amenoreli hastalardaki parsiyel androjen duyarsızlık sendromu prevalansının belirlenmesi ve 8 olgunun incelenmesi. **Gereç ve Yöntemler:** Retrospektif olarak 2005 yılındaki primer amenoreli adolesan hastaların kayıtlarını, parsiyel androjen duyarsızlık sendromlu hastaların prevalansını belirlemek için gözden geçirdik. Ayrıca 2003-2005 yılları arasında, parsiyel androjen duyarsızlık sendromu tanısıyla 7'sinin gonadları alınan 8 hastanın dosyalarını inceledik. Asıl yakınmalarını, klinik ve laboratuvar bulgularını, cerrahi sırasındaki bulgularını, postoperatif patoloji bulgularını ve gonadektomi sonrası tedavilerini gözden geçirdik ve tartıştık. **Bulgular:** 2005 yılında 725 hasta adolesan jinekolojisi birimine adet düzensizliği yakınmasıyla başvurdu. Bunların 39 (%5.12)'unda primer amenore mevcuttu. Bu 39 hastanın 2 (%5.12)'sinde 46 XY karyotipi saptandı. Bunlardan biri testiküler feminizasyon (tam androjen duyarsızlık sendromu), diğeri (%2.56) psödohermafrodit (parsiyel androjen duyarsızlık sendromu) idi. 2003-2005 yılları arası 8 olgudan 7'sinin gonadları alındı. Bir hasta için, yaşının 10 olması nedeni ile gonadektomi puberte sonrasında planlandı. **Sonuç:** Androjen duyarsızlık sendromunun prevalansı genellikle canlı doğumlara oranlanarak verilir. Biz, klinik pratikte, prevalansın primer amenoreli hastalara oranlanmasının daha yararlı olacağını düşünüyoruz. Kromozom incelemesi primer amenoreli artmış gonadotropin düzeyleri olan her hastada yapılmalıdır. Parsiyel androjen duyarsızlık sendromunun genel tedavisi puberte sonrası gonadların çıkarılması ve hormon yerine koyma tedavisidir. Ancak, danışmanlık ve psikolojik takip hastaya yaklaşım protokolünün esas bileşenleridir.

Anahtar Kelimeler: Androjen duyarsızlık sendromu; yalancı hermafroditizm; puberte; hormon replasman tedavisi

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Androgen insensitivity syndrome (AIS) is an X-linked disorder caused by an abnormality of the gene for the androgen receptor in 46,XY individuals. More than 100 different gene defects, including deletions and point mutations, have been described.[1] It presents a wide spectrum of clinical manifestations that has allowed its classification into complete, and partial forms as well as a rare group of phenotypical men with azoospermia.

The complete form of AIS, sometimes referred to as classical testicular feminization, is characterized by external female phenotype with absent or scanty pubic and axillary hair, absence of the uterus and ovaries, intraabdominal testes, blind ending vagina and gynecomastia.[2] The prevalence is estimated at between 1 in 20.000 and 1 in 60.000 live births.[3]

Partial AIS is less common. The presentation includes ambigous genitalia at birth, with clitoral enlargement and fusion of labioscrotal folds. Virilization occurs at puberty to a degree that depends on the activity of the androgen receptor.[4]

The incidence of neoplasia in these gonads is high. Therefore, once full development is attained after puberty, the gonads should be removed.[5]

In this report, we present 8 patients with partial AIS, 7 of whose gonads are removed. We discuss the diagnosis, management and associated conditions of this rare syndrome.

MATERIAL AND METHODS

We retrospectively reviewed the records of adolescent gynecology unit of our hospital, in order to determine the prevalence ratio of patients having 46 XY karyotype among the primary amenorrheic patients. We gave the results as percentages.

We have retrospectively reviewed the files of 7 patients whose gonads were removed with the diagnosis of partial AIS syndrome between the years 2003-2005. Their chief complaints, clinical and laboratory findings, findings at operations, postoperative pathologic findings and treatment after gonadectomy were reviewed and discussed. In addition, a 10 years old patient referred to our hospital with the diagnosis of pseudohermaphroditism is also diagnosed as having partial AIS, and gonadectomy is planned after puberty.This girl is the sister of the one of our patients with gonadectomy. This patient's characteristics are also presented.

RESULTS

During the year 2005, 725 patients applied to adolescent gynecology unit with the complaint of menstrual irregularities. Thirty-nine (5.37%) of 725 had primary amenorrhea. Among 39 patients 2 (5.12%) had 46 XY karyotype; one was testicular feminization (complete AIS) and one (2.56%) was pseudohermaphroditism (partial AIS).

Some of the characteristics of AIS patients, clinical and laboratory findings, ultrasonographic findings, chromosome analysis and postoperative pathologic findings are presented in Table 1. We presented all cases in brief, as follows:

CASE 1

The patient was 22 years old. Her chief complaint was the absence of menarche. There was a mild clitoromegaly. She had a normal appearing but short vagina. Her preoperative evaluation by ultrasonography yielded presence of two gonads without uterus. Laparoscopy showed the presence of hypoplastic uterus, streak gonad on the right, and 2 x 1 centimeter sized left gonad with bilateral normal appearing salpinges. Bilateral salpinges and gonads removed, laparoscopically. Pathological examination showed that the removed gonads were testes with tubular sclerosis and Leydig cell hyperplasia. The patient is now receiving hormone replacement therapy.

CASE 2

The patient was 27 years old, amenorrheic with the absence of vagina. She had normal sized clitoris. Her uterus and gonads were not seen on ultrasonography. Laparoscopic examination showed 2 x 1 centimeter sized gonad on the right, and 2 x 2 centimeter sized gonad on the left next to external iliac vessels, and they were removed. There was no uterus. Hormone replacement therapy was started after the operation. The right gonad was atrophic testis, and there was tubular cyst on the left, by pathological examination.

TABLE 1: Partial androgen insensitivity syndrome patients' characteristics.

Name	Age	Chief complaint	Usg	Clitoromegaly	Vagina	Fsh	Testo-sterone	Karyotype	Pathology
Case 1	22	Primary Amenorrhea	Uterus (-) Gonads (+)	Present	Present short	78	41	45X,46XY	Testes, tubular sclerosis, Leydig cell hyperplasia
Case 2	27	Primary Amenorrhea	Uterus (-) Gonads (-)	Absent	Absent	21	10.4	46XY	Right atrophic testis, left tubular cyst
Case 3	16	Primary Amenorrhea	Uterus (-) Gonads (-)	Present	Absent	11	4	46XY	Testes and epididymides
Case 4	23	Primary Amenorrhea	Uterus (+) Hypoplastic Gonads (+)	Absent	Present normal	81	-	46XY	Right dysgerminoma Lymphovascular invasion (-) Left streak gonad
Case 5	18	Primary Amenorrhea	Uterus (-) Gonads (-)	Present	Absent	-	-	46XY	Bilateral testes and Epididymides
Case 6	30	Primary Amenorrhea	Uterus (-) Gonads (-)	Present	Present short	9.5	7.8	46XY	Atrophic testes
Case 7	18	Primary Amenorrhea	Uterus (-) Gonads (-)	Present	Present normal	20.9	21	46XY	Bilateral testes
Case 8	10	Pseudoherm aphroditism	Uterus (+) Gonads (+)	Present	Present short	0.08	0.06	46XY	-

CASE 3

The patient was 16 years old, amenorrheic girl with mild clitoromegaly. Her vagina was absent. Gonads were palpable in the inguinal region, bilaterally. Ultrasonography showed no uterus and gonads, intraabdominally. The operation was performed by bilateral inguinal incisions, and gonads were removed. Pathological examination revealed testes and epididymides. She receives estrogen replacement therapy, currently. And she is planned to have vaginoplasty in the future, when necessary.

CASE 4

The patient was 23 years old, amenorrheic girl with normal vagina and clitoris. Ultrasonography showed the presence of hypoplastic uterus with gonads. During laparoscopy, a band-like uterus with 2 x 1 centimeter sized gonad on the right, and a streak gonad on the left were seen. Both gonads were removed with bilateral salpinges. Pathological examination resulted in dysgerminoma of the right gonad without lymphovascular space invasion, with left streak gonad. She is using hormone replacement therapy following the surgery.

CASE 5

The patient was 18 years old, amenorrheic girl with the absence of vagina. She had mild clitoromegaly. Gonads were palpable under labial folds. Ultrasonographic examination showed no uterus or gonads. Gonads were removed bilaterally, by bilateral inguinal incisions. Pathological examination showed bilateral testes and epididymides. She is now on hormone replacement therapy.

CASE 6

The patient was 30 years old, single, amenorrheic girl with a short vagina. She had mild clitoromegaly. Her gonads were palpable under the skin of both inguinal regions. Ultrasonography revealed absence of uterus and gonads. Bilateral gonadectomy was done by two inguinal incisions. Pathological examination showed bilateral atrophic testes. She is taking hormone replacement therapy, currently.

CASE 7

The patient was 18 years old, single, amenorrheic girl with a normal vagina. She had clitoromegaly, but she have been operated for clitoromegaly, a year ago. Her uterus and gonads were absent, on ul-

trasonographic examination. There were two gonads palpable on both inguinal regions. Gonads were removed by two inguinal incisions. Pathological examination revealed bilateral testes. She uses hormone replacement therapy.

CASE 8

The patient was 10 years old girl, referred to our unit with the diagnosis of pseudohermaphroditism. She is the sister of the girl presented as case 7. She had a short vagina with mild clitoromegaly. Ultrasonographic examination showed a small uterus and small prepubertal gonads. She was planned to have gonadectomy after puberty.

DISCUSSION

Androgens play a crucial role in the development, maintenance and regulation of the male phenotype and reproductive physiology. This role is mediated by the intracellular androgen receptor which consists of 910-919 amino acids and is encoded by a gene with 8 exons located in Xq11-12. Testosterone or dihydrotestosterone binding induces a trans-conformation of the androgen receptor and allows its translocation into the nucleus, where it recognizes specific DNA sequences.[2] In androgen insensitivity syndrome, defects in the androgen receptor gene prevent the normal development of both internal and external male structures in 46 XY individuals. Most variations in the androgen receptor gene are point mutations inhibiting either hormone or DNA binding. In two thirds of all cases, these mutations are inherited from mother, while the rest occur as a result of a spontaneous mutation in the egg/zygote.[2]

Although testosterone is produced in these individuals, androgen receptor defects permit the development of female external anatomy, whereas the actions of mullerian inhibiting substance prevent the development of the uterus, fallopian tubes and proximal vagina. These patients are infertile, and at risk for gonadal malignancy. Patients are raised as girls, and the diagnosis of androgen insensitivity syndrome is usually not made untill amenorrhea is investigated.[6]

The prevalence of complete androgen insensitivity syndrome is estimated to be 1 in 20.000 and 1 in 60.000 live births.[3] However, it is more frequently seen among the girls with inguinal hernias. In one study, the incidence of complete androgen insensitivity in girls with inguinal hernias are reported to be 1.1%.[6]

Saatçi et al. reported that chromosomal abnormalities was present in 21% of patients with primary amenorrhea. Thirty-four percent of the chromosomal abnormalities was 45,X and 23% was 46,XY. So, they found that 4.83% of the patients with primary amenorrhea had 46,XY karyotype.[7] We found this figure as 5.12% from the records of adolescent gynecology unit of our hospital in 2005. By these results we can conclude that among primary amenorrheic patients 1 of 5 had chromosomal abnormalities and 1 of 20 had 46,XY karyotype. Therefore, chromosomal analysis in patients with primary amenorrhea should be done to diagnose the etiology, especially in patients with elevated gonadotropin levels.

Clinical manifestations of androgen insensitivity syndrome are usually inguinal hernia, amenorrhea, infertility and positive family history. There are three AIS phenotype classifications: complete androgen insensitivity syndrome (CAIS), also known as testicular feminization, partial androgen insensitivity syndrome (PAIS), and mild androgen insensitivity syndrome (MAIS), also known as under-virilized male syndrome.[8]

Diagnosis is usually made with the absence of uterus on physical exam and pelvic ultrasonography, karyotyping, elevated testosterone levels, molecular genetic testing of the androgen receptor gene mutations.[9]

The location of the gonads can be variable including, the intraabdominal cavity, the labioscrotal folds, and the inguinal regions. Studies have found that gonad position correlates with the degree of androgen insensitivity. The incidence of abdominal testes is, highest in patients with CAIS who are phenotypically female with scant pubic hair, and it decreases with increasing degree of masculinization.[10]

Management of AIS consists of counseling, psychological support, surgery and hormone replacement therapy.

Migeon CJ, et al. reported that almost half of 46,XY, intersex individuals, reared male or female, had been neither well informed about their medical and surgical history nor satisfied with their knowledge.[11] One major challenge in the management of the patients, reared female, is in disclosing the gender and fertility implications to them. Few crises can be as overwhelming as the prospects of congenital childlessness in an environment that places high premium on fertility. Counseling and psychological follow-up are therefore essential components of the management protocol.[2]

Surgery is required for gonadectomy and in some patients to increase the vaginal length. Timing of gonadectomy either prepubertal or postpubertal is controversial. However, most authors suggest the postpubertal gonadectomy because the natural female pubertal changes are dependent on the conversion of testosterone to estrogen.[2,5,12] Although the incidence of malignancy is reported to be 5 to 22%, gonadal tumors in these patients are not encountered before puberty. Therefore, once the full development is attained after puberty, the gonads should be removed at approximately age 16-18, and the patient should receive hormone therapy.[5] The disadvantage of prepubertal gonadectomy is the immediate need and compliance of the patient for estrogen replacement therapy to maintain feminization and avoid premature osteoporosis.[12] On the other hand, if testes are in the inguinal canal causing pain or hernias, then prepubertal gonadectomy is indicated and estrogen replacement is required.[12]

CONCLUSION

The prevalence of androgen insensitivity syndrome is usually given as the ratio among live births. We think that prevalence among primary amenorrheic patients will be more useful in clinical practice. Chromosome analysis should be done in every patient with primary amenorrhea having elevated gonadotropin levels. The usual treatment for partial androgen insensitivity syndrome is gonadectomy after puberty and hormone replacement therapy. However, counseling and pschological follow-up are essential components of the management protocol.

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