To Which Gender Should External Genitalia be Corrected in a Lately Diagnosed 46,XX Congenital Adrenal Hyperplasia Case with Severe Virilization: Case Report

Geç Tanı Almış İleri Derece Virilize 46,XX Konjenital Adrenal Hiperplazide Cinsiyet Hangi Yönde Düzeltilmeli?: Bir Olgu Nedeniyle

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ABSTRACT The most common cause of disorders of sexual development in which external genitalia and/or secondary sexual charecteristics could not be differentiated either as male or female is congenital adrenal hyperplasia (CAH). The most common cause of congenital adrenal hyperplasia, 21-hydroxylase deficiency, is related with masculinization of external genitalia and behaviours. Here we present a severely virilized, lately diagnosed 46, XX CAH case who was reared as male and referred to our pediatric endocrinology department for gender reassignment. The five-year-old patient applied to prior pediatric endocrinology clinic with the complaints of acne, deepening of voice and hair development at pubic region and legs. Considering physical and laboratory evaluations and imaging, the diagnosis of 46,XX CAH due to deficiency was made. Even a 46,XX CAH patient develops excessive virilization in newborn period, common practise is rearrangement of the gender almost always in the direction of female. However there remains a lack of consensus for assigning the gender in cases who are lately diagnosed. Some of the CAH cases who are diagnosed after two years of age are not satisfied with their previously established female gender thus continue their rest of lifes adopting a male gender. A multidisciplinary approach is required in evaluation and treatment stages of such cases. In order to prevent late diagnosis, a careful physical examination should be done and subsequently, patients having ambiguous genitalia should be referred to pediatric endocrinology clinics. Thus such cases will be diagnosed prior to development of their gender identity and treatment can be provided in time.

Key Words: Disorders of sex development; adrenal hyperplasia, congenital; sex determination processes

ÖZET Genital organların ve/veya ikincil seks özelliklerinin dişi veya erkek olarak sınıflanamadığı cinsiyet gelişim bozukluğu olgularının en sık nedeni konjenital adrenal hiperplazidir (KAH). En sık KAH nedeni olan 21-hidroksilaz eksikliği 46,XX bireyde genital organların ve davranışın maskülinizasyonu ile ilişkilidir. Burada, geç tanı alan ve cinsiyet düzenlenmesi talebiyle polikliniğimize yönlendirilen, ileri derecede virilize, erkek olarak büyütülmüş bir 46, XX KAH olgusu sunulmuştur. Beş yaşındaki çocuk ilk olarak; akne, seste kalınlaşma, pubiste ve bacaklarda kıllanma şikayetiyle endokrinoloji polikliniğine götürülmüş. Bölümümüze yönlendirilen hastaya; fizik inceleme, laboratuvar analiz ve görüntüleme sonuçlarına göre 21-hidroksilaz eksikliğine bağlı 46,XX KAH tanısı konuldu. 46,XX KAH olgularında, yenidoğan döneminde, aşırı virilizasyon olsa bile, uygulama olgunun cinsiyetinin hemen her zaman dişi yönünde düzenlenmesi şeklindedir. Fakat geç tanı alan bu tip vakalarda cinsiyetin hangi yönde düzenleneceği konusunda ortak bir konsensus oluşturulamamıştır. İki yaşından sonra tanı alan 46,XX KAH olgularının bir kısmı dişi olarak düzenlenen cinsiyetlerinden rahatsızlık duymakta ve erkek olarak yaşamlarını sürdürmektedir. Multidisipliner yaklaşım bu tür vakaların değerlendirilmesi ve tedavisinde önemlidir. Bu nedenle geç tanıyı önlemek için her bebeğe doğar doğmaz dikkatli bir genital muayene yapılmalı, cinsiyetinde kuşku duyulan bebekler ivedilikle ilgili merkezlere yönlendirilmelidir. Böylelikle cinsiyet gelişim bozukluğu saptanan bu olgular erken tanı alarak cinsel kimlikleri oluşmadan tespit edilecek ve tedavileri zamanında yapılabilecektir.

Anahtar Kelimeler: Cinsiyet gelişim bozuklukları; adrenal hiperpilazi, doğumsal; cinsiyet tayini işlemleri

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21-hydroxylase deficiency is the most common cause of disorders of sex development (DSD) in patients with 46,XX karyotype. Deficiency of this enzyme leads to a decrease in cortisol level thus a compensatory increase in ACTH level further stimulates the adrenal androgen production. Even excess androgen production does not usually affect internal genitalia development of 46,XX, however it causes virilization of external genitalia.[1] In this paper we report a lately diagnosed child with puberty precocious who developed complete masculinization of external genitalia due to deficency type of CAH. In such cases consideration about gender assignment is very important. Even the patient was severely virilized during infancy, the common consideration is establishing the external genitalia of the patient in female gender. Some of the CAH cases who are diagnosed after two years of age are not satisfied with their previously established female gender thus continue their rest of lifes adopting a male gender.[2] Whether delay of genitoplastic intervention in early childhood till the time that patient makes her own consideration about her gender is more acceptable or not is still contraversial.[3] After feminizing genitoplasty operation done in early childhood, request for reassignment of gender as a male is very rare.[4] In this report we discuss gender assignment in a lately diagnosed 46,XX CAH case due to 21-hydroxylase deficency.

CASE REPORT

A 5-year-old child admitted to our endocrinology department with the complaints of pubic hair, deepening of voice and acne development. The child was being reared as male and born to consanguineous parents, with two healthy sisters and a brother. There was no family history of CAH. Psychometric development was consistent with 3 years of age. Physical examination was as follows: height 130.4 cm (>97 percentile), weight 35.6 kg (>97 percentile), height age 9 years, bone age 13 years (Greulich and Pyle atlas) and blood pressure 90/60 mmHg. The child had axillary and pubic hair (Tanner stage III). Widespread acne, hoarseness, muscle hypertrophy and genu valgum deformity were also present. The phallus was 7 cm in length and with a normal urethral meatus on the glans. Gonads were not palpable in scrotum or in inguinal canals, and the scrotum was hyperpigmented (Figure 1). There was no gynecomastia. Karyotyping revealed 46,XX chromosome. On biochemical examination, serum electrolytes, glucose, liver and renal function tests were normal. Hormonal tests were as follows; 17 alpha-hydroxyprogesterone 25 ng/ mL (0.1-0.9), 11-deoxycortisol 0.82 ng/ml (< 0.94), cortisol 2.51 µg/dL (5-25), total testosterone 20.5 ng/mL (0.15-0.6), ACTH 991 pg/mL (0-60), DHEAS 219 µg/dl (98.8-340), androstenedione 13.9 ng/ml (0.21- 3.08) and renin 65 pg/ml (5-27.8). Pelvic ultrasound examination showed the presence of uterus (23×17×35 mm) and ovaries (23×10, 23×13 with multiple follicular cysts). Both adrenal glands were found to be hyperplasic on the abdominal ultrasonagraphy.

Based on these findings, a final diagnosis of simple virilizing CAH due to deficiency of 21-hydroxylase in a genotypic female was made and hydrocortisone treatment was started. The decision of the family about the gender assignment of their child was to raise her as a male. Thus the patient is awaiting hysterosalpingooophorectomy and insertion of prosthetic testicles. GnRH analogue treatment was considered in order to slow her puberty untill the surgical removal of uterus and ovaries. Written consent was obtained from the patient or relative for publication of this study.

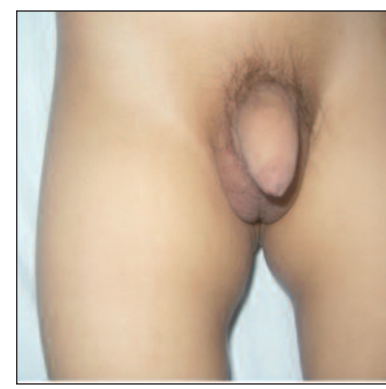

FIGURE 1: Prader stage V virilization, hyperpigmentation and signs of early puberty.

DISCUSSION

21-hydroxylase deficiency which leads to abnormally low cortisol level and increased production of androgen precursors is the most common cause of ambiguous genitalia and accounts for 90% of CAH cases. Excessive adrenal androgens in these patients during the 11th week of fetal development lead to hypertrophy of clitoris, variable virilization of the urethra and fusion of the labioscrotal folds. But in a female fetus with CAH, normal development of the female internal urogenital tract occurs.[1] Preestablished criterias do not exist for cases who are lately diagnosed. It was already reported that 46,XX CAH cases who are reared as female shows more masculine behaviours in their body language when compared to healthy females. [5-7] It was suggested that these masculine behaviours are related with the magnitude of prenatal androgen exposure and the degree of defects both in the enzyme and virilization in genital organs.[7] Prenatal, postnatal and perinatal androgenization, and enviromental factors are important issues in the development of sexual identity. Our case possesses masculine behaviours accompanied by advanced virilization (prader V). Her childhood games, body language and choice of profession are compatible with male gender. It was suggested that prenatal androgens have effects on both sexual identity and orientation. However this probable interaction is not constant since some of the 46,XX CAH cases who possesses masculine behaviours request rearrangement of their sexual identity who already assigned as female whereas remainder majority do not complain about their gender identity.[8,9] The association between genitalial masculinization and virilization of brain could not completely be defined yet. Moreover some authors proposed that sexual differentiation of the brain spreads to the first 5 years of life and processes occuring in this period are independent from the development of external genitalia.[4] Because of her first application at 5 years old and realization of his male gender adoption during her child psychiatric evaluation, and finally in regard to guidance of child psychiatry which is compatible with the consideration of her family, the patient underwent male reconstructive surgery. A severely virilized CAH case who was raised as male untill school age assigned as female at that time but afterwards refused female gender.[10,11] That case is alike our case because of her severe virilization and delayed diagnosis. However our case underwent male reconstructive surgery unlike that case. Our patient does not have a long standing follow up yet. Jorge et al.[12] reported a 46,XX CAH case born with Prader III level virilization and underwent female reconstructive surgery at 20 months old of age, and now living with heterosexual male gender identity. This case also could not fit into female gender and the reason for this incompatibility was noted as insufficient suppression of adrenals after diagnosis. However a consensus still could not be built for gender assignment in 46,XX CAH cases who were lately diagnosed. Some of the CAH cases who are diagnosed after two years of age are not satisfied with their previously established female gender thus continue their rest of lifes adopting a male gender. Therefore a multidisciplinary approach including child psychiatry, pediatric endocrinology, pediatric surgery and genetics is required in the evaluation of these cases.[12]

Gender identity emerges by the age of two. Child realizes itself male or female and makes her choices about toys, clothes, colleagues and games that are congenial with her gender identity. By the end of age one, gender-compatible genitalial reconstructive surgery can be done untill the age of two. Misassignment of child's gender and being over 3-4 years of age brings a lot of troubles in further life of the child. It is usually impossible to change the gender of the child in the opposite direction after 3-4 years of age. Gender correction in 46,XX disorders of sexual development cases due to CAH is everchanging by the increase in our understanding about the biopsychosocial dimensions of gender. It is also certain that this issue does not have clear rules. At that point, early diagnosis of CAH is the chiefpoint to prevent the further physiological insults of the disease on child and the psychosocial ones on both child and parents. Moreover genitalial reconstructive surgery at that time will

be much easier and more successfull. However all of these cases could not receive early diagnosis. Therefore a multidisciplinary approach is required in the assessment of lately diagnosed 46.XX, 21-hydroxylase deficiency patients and particularly the evaluation of child psychiatry will play a crucial role in the final consideration of gender assignment.[12] Although consanginous marriages are not so common unlike in Turkey, CAH screening is routine in some european countries and United States. However these programs are expensive and may not work properly due to lack of 17 hydroxyprogesterone measurement via extraction method even in developed countries. Therefore careful genital examination at primary and secondary health services at birth and later follow-up is the cornerstone for early diagnosis of a 46,XX CAH case.

As a consequence, examination of external genitalia should be done in every newborn at birth and subsequent referral of a baby with a consideration of ambiguous genitalia to an endocrinology clinic should be performed. Thereby early diagnosis will lead to detection of a 46,XX CAH case due to 21-hydroxylase deficiency before development of gender identity and enable to provide required treatments in time otherwise this dilemma will become even more complicated. As in our patient, such patients with delayed diagnosis requires multidisciplinary approach and consideration of child psychiatry is particularly important in terms of gender assignment.

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