Case Report of an Adult Patient with Hypospadias, 46,XX Maleness and 21-Hydroxylase Deficiency – Coincidence or Association?

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ABSTRACT

Introduction and Objectives. The most common cause for Congenital adrenal hyperplasia (CAH) is due to 21-hydroxylase deficiency which can produce disorders of sex development. 46,XX maleness is a rare syndrome with an incidence of 1 in 20000-25000 males, and they are defined by ambiguous genitalia or partially to fully mature male genitalia.

Materials and Methods. We present the case of a 49-year-old patient (46,XX) with CAH resulting from 21-hydroxylase deficiency, diagnosed with penoscrotal hypospadias at the age of 3 and a half years for whom multiple corrective surgeries were performed and was referred to our hospital for evaluation of urethrocutaneous fistulas.

Results. In 2021, the patient was diagnosed by the endocrinology department with 46,XX Karyotype, male phenotype and congenital adrenal hyperplasia due to 21 hydroxylase deficiency. The urological diagnosis established at "Prof. Dr. Theodor Burghele" Clinical Hospital was of multiple urethrocutaneous fistulas that occurred after penoscrotal hypospadias repair in childhood. The surgical indication consisted of urethroplasty with oral mucosa graft in two steps, the time between interventions being about four months. The surgical evolution was good, without complications. Complications after multiple times operated hypospadias are redoubtable, including strictures of the anterior urethra, urethral fistulas, urethritis, and recurrent urinary tract infections. The treatment of such cases is particularly difficult.

Conclusions. The use of extragenital tissues for urethral reconstruction (oral mucosa graft) provides superior functional and aesthetic results compared to the techniques using skin flaps.

Key-words: 46,XX, 21-hydroxylase deficiency, hypospadias.

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INTRODUCTION AND OBJECTIVES

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder and the most common cause is 21-hydroxylase deficiency that is characterized by glucocorticoid and mineralocorticoid deficiency and androgen excess and can produce disorders of sex development. 21-hydroxylase deficiency is a congenital defect that is coded by the CYPA21A2, and results in impaired cortisol biosynthesis with adrenal insufficiency and hyperandrogenism [1].

Some of the children with CAH and 46,XX genotype stay under androgen overexposure, and their external genital organs appear to be virilized in 90% of cases. In this situation, most of these patients are raised as a male and they are diagnosed late [2]. The rest of 10% of the cases that are SRY (sex-determining region Y) negative are presenting hypospadias, undescended testes, and other forms of inadequate virilization. Other characteristics are short stature, gynecomastia, infertility, hypogonadism, and normal mental health development [3].

The Consensus statement on the management of intersex disorders published in 2006 considers that the 46,XX CAH patients should be raised as females and that severe virilization is not a criterion for male sex determination [4]. However because most of these patients are diagnosed late in countries without a screening program for the disorder, they tend to be raised as males [5].

Hypospadias is one of the most common congenital malformations and occurs in 1 out of 150 to 300 live births [6]. It is described as an abnormal displacement of the urethral meatus to the ventral side of the penis [7].

The urethral folds fail to completely or partially close, and foreskin does not fuse onto the ventral aspect of the penis. The etiology of hypospadias is still unknown but several explanations have been considered, including genetic abnormality, hormonal influence, and environmental factors [8].

MATERIALS AND METHODS

A 49-year-old male with penoscrotal hypospadias diagnosed at the age of 3.5 years and corrected 5 years later, was referred to our hospital for evaluation of multiple urethrocutaneous fistulas.

In 2021, the patient was diagnosed with Congenital Adrenal Hyperplasia (CAH) due to 21 hydroxylase deficiency at the age of 49 years. After chromosomal analysis by the endocrinology department, it was revealed a 46,XX karyotype, maleness. This was followed by a metaphase FISH using Leica CW4000 CytoFISH for the SRY gene. Twenty metaphases were evaluated and the Y chromosome was not visualized. The karyotype was 46,XX.ish X (DXZ1x2, DYZ1x0, SRYx0, wcpXx2, wcpYx0).

Endocrinology laboratory evaluation revealed a serum follicle-stimulating hormone (FSH) level of 60.81 mIU/mL (normal male level:1.5 to 12.4) and LH level of 33.46 mIU/mL (normal male level: 1.7 to 8.6), testosterone serum level was 1,71 ng/mL (laboratory limit 1.75-7-81).

At physical examination, the patient's height was 146 cm, and weight was 57 kg. The chest examination revealed no gynecomastia. At skin evaluation is noted light facial hair growth and pubic hair was normal (Tanner stage V). The genitalia examination revealed that stretched penile length was 5 cm with multiple urethrocutaneous fistulas (after the correction of penoscrotal hypospadias). The scrotum was hypoplastic with a nonpalpable gonad bilateral.

RESULTS

Magnetic resonance imaging (MRI) of the pelvis confirmed the presence of a hypoplastic uterus, two ovaries/ovotestis, a small prostate (24/20/20 mm), and no testis were identified.
A preoperative retrograde urethrocystogram was performed. The contrast substance was introduced through one of the urethrocutaneous orifice and opacifies the urethra (with a narrowing at the

bulbo-membranous segment), the urogenital sinus, the vagina, and the bladder. The junction between the urethra and the female genital organs seems to occur at the level of the bulbar urethra.

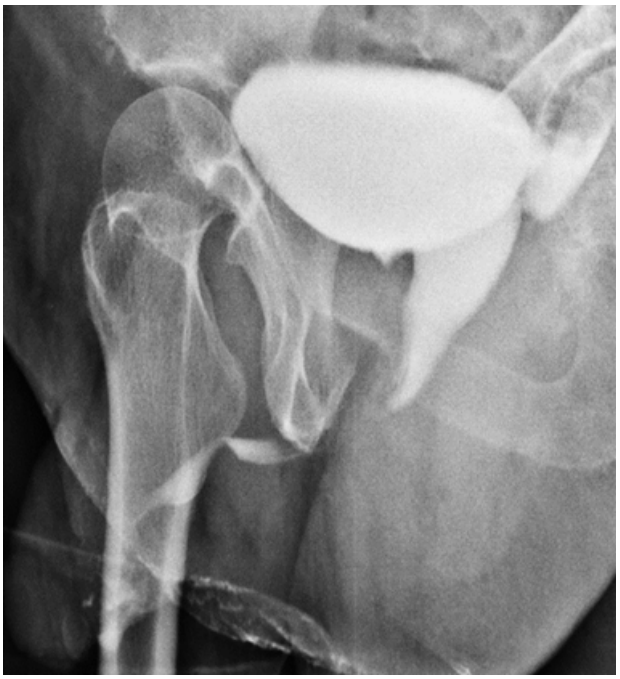


Figure 1 - Retrograde urethrocystogram

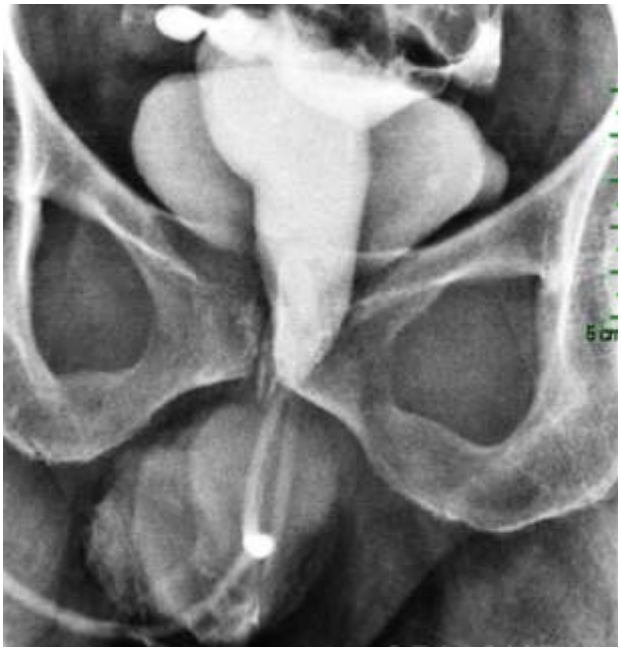


Figure 2 - Retrograde urethrocystogram with the presence of urogenital sinus, vagina, and bladder

Urethrocystography in this case determines the configuration of the urethra, the position of the confluence between the urethra and genital canal, and the bladder appearance. According to Prader's classification, all these examination findings suggested the 4th degree of virilization for the patient.

At 9 years old the penoscrotal hypospadias was repaired using skin flaps. In 2021 the patient presented with multiple urethrocutaneous fistulas situated at the glans and base of the penis.

Two-stage urethroplasty with buccal mucosal graft was performed with the complete excision of the urethral segment with scar tissue and hair.



Figure 3 – Urethrocutaneous fistula

The second stage of urethroplasty was performed after 4 months. The patient had a successful outcome without complications and no recurrent stricture with a mean postoperative peak flow rate of 19 ml. per second.

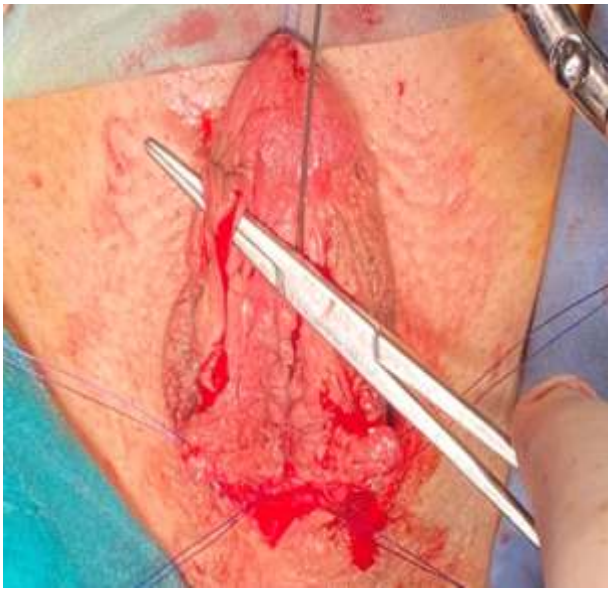


Figure 4 – Intraoperator aspect of the urethra with the highlighting of the fistulous path

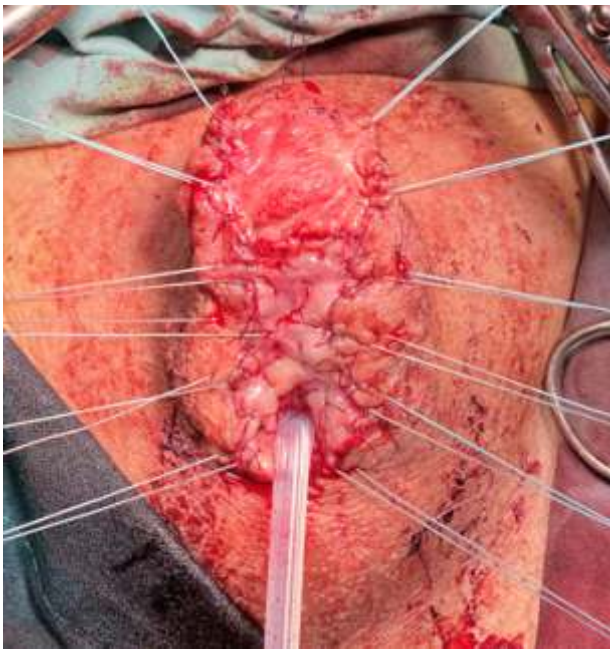


Figure 5 – First stage of urethroplasty



Figure 6 – The final result after two-stage urethroplasty with buccal mucosal graft

DISCUSSIONS

The diagnosis of congenital adrenal hyperplasia is usually delayed because of the lack of newborn screening programs in most countries [9]. The late diagnosis can be an unfortunate consequence of the extent of virilization that corresponds to the 4th or 5th degree according to the classification of Prader [10]. Recognizing these patients is extremely important and the most common signs are bilaterally empty scrotum with or without hypospadias urethral meatus and bilateral gynecomastia [11].

It is recommended by physicians that patients diagnosed early in life to be raised as girls and surgical procedures should be performed as soon as the gender is assigned [12]. The ideal choice of surgery is feminizing genitoplasty for early-diagnosed cases [13].

In case of delayed diagnosis or the family decision to raise these patients as males the surgical procedures consist of hysterectomy, bilateral salpingo-opherectomy, testicular prosthesis, and reduction mammoplasty depending on the case [14].

This case illustrates that true hermaphroditism may present in adulthood in patients who were raised as men by their families due to the absence of diagnosis at birth. Considering the advanced age of the patient at diagnosis, it was established that he does not require surgical intervention to remove the internal genital organs. After multiple discussions with the patient, the decision was made to treat only the complications that occurred after the hypospadias surgery.

Two-stage urethroplasty with buccal mucosa is commonly indicated for patients with highly complex strictures following failed hypospadias repair and it has low recurrence rates [15].

The diagnosis of CAH in an adult, with severe virilized external genitalia, that has been raised up to be a man, will have an important psychological impact. The data regarding this problem is scant, and it shows that these patients have a higher risk of suicide [16].

CONCLUSIONS

In our case the particularity was the late diagnosis age of the disorder of sex development and the importance of treating the complications arising after the surgical treatment of hypospadias, which interfered with the patient's normal day-to-day life. The use of extragenital tissues for urethral reconstruction (oral mucosa graft) provides superior functional and aesthetic results compared to the techniques using skin flaps.

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