

# Two-step surgery for a unique case of idiopathic female pseudohermaphroditism

## Surgical treatment in an exceptional combined uro-genital malformation



Ann. Ital. Chir., 2012 83: 571-575  
pii: S0003469X12018246

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**Two-step surgery for a unique case of idiopathic female pseudohermaphroditism. Surgical treatment in an exceptional combined uro-genital malformation.**

*A 15 years-old patient was brought to our attention in June 2010 with a complex genito-urinary malformation: fusion of the labia majora and a partial union of labia minora, common urinary and vaginal meatus and clitoromegaly. The patient had a normal sexual feminine hormonal development. After diagnostic iter the patient underwent surgery twice. No signs of hormonal deficiency was shown authorizing us to approach the disease as a congenital malformation due to an abnormality of intrauterine development. So surgical treatment was carried out, considering it as the gold standard for this type of malformations.*

*It's considerable to emphasize that the association between clitoromegaly and fusion of the lower third of the urethra with the vagina has not been previously reported in the literature.*

**KEY WORDS:** Genitalia anomalies, 21- $\beta$ -hydroxylase deficiency, Idiopathic female pseudohermaphroditism, Surgical treatment.

### Introduction

Congenital genitalia anomalies are a spectrum of malformation, characterized by different anomalies affecting all uro-genital structures. A univoque classification of these disorders is difficult because similar or identical phenotypes could have several different aetiology. Frequently it is not possible to correlate the disorder aetiology with the appearance of the external genitalia<sup>1-4</sup>.

Patients with female pseudohermaphroditism have XX karyotype, female internal genitalia but a variety of external

genitalia virilization signs. Congenital adrenal hyperplasia (CAH) is mostly caused by 21- $\beta$ -hydroxylase deficiency, but every deficiency along estrogen enzymatic cascade can determine an analogue phenotype. Another possible cause for female pseudohermaphroditism is a maternal androgen excess due to maternal ovarian tumor or drug intake.

It is an uncommon condition (less than 1/10,000), and may be familial or sporadic. Criteria applied to reach a diagnostic are karyotype, hormones and derivatives investigation, genital ultrasound and endoscopy, where necessary radiological examinations are added to diagnostic iter. It is important to emphasize the diagnostic difficulties, as in this case reported, that often lead to a wrong or delayed diagnosis. It is, then, essential to develop a therapeutic strategy, including medical or surgical treatment or a combination of both.

We report the case of a patient affected by a rare form of pseudohermaphroditism suggesting the diagnostic iter

*Pervenuto in Redazione Settembre 2011. Accettato per la pubblicazione Novembre 2011*

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that allowed us to reach at a correct diagnosis and the difficulty to clearly understand anatomical features of this complex uro-genital anomaly<sup>5,6</sup>. The particularity of the reported case is that the association between clitoromegaly and the presence of a fusion of the lower third of the urethra with the vagina has not been previously described. We also describe the surgical technique and the excellent aesthetic result we obtained. We stress on the improvement in psychological profile of the young patient.

## Case Report

A 15 years-old patient was brought to our attention in June 2010 with a complex genito-urinary malformation. The patient, previously admitted in her country with 21-beta-hydroxylase deficiency diagnosis was hospitalized to our ward. Because it was taken for granted previously made diagnosis of 21- $\beta$ -hydroxylase deficiency, it led astray in the initial treatment. At the examination the patient showed a fusion of the labia majora and a partial union of labia minora, in addition she presented a common urinary and vaginal meatus. She also showed

a clitoromegaly (4,5 cm). The patient had a normal sexual feminine hormonal development and reported the menarche at 14 years old (Fig. 1).

The patient had a painful family history, was isolated by the family due to malformation, lived in a halfway house and was not able to relate to the medical staff. In addition not being able to understand Italian was accompanied by an interpreter. Her mood was of shame and feelings of inadequacy.

The patient was then subjected to a series of hormonal analysis to determine malformation etiology. Blood tests showed no significant alterations, hormonal tests (FSH, LH, ACTH, 17-oh progesterone, DEHA sulfate, testosterone, prostaglandins, cortisol) showed no changes significant for a 21- $\beta$ -hydroxylase deficiency. She was also tested with Synacthen stimulation for the 17-OH-progesterone production without any evidence of alteration (Table I).

In addition, the MRI did not show any alterations of the adrenal cortex that could point towards a diagnosis of 21- $\beta$ -hydroxylase deficiency.



Fig. 1: Pre-operative aspect of external genitalia.



Fig. 2: Urography showing an abnormal vaginal captation.

TABLE I - Blood tests and hormonal tests showed no significant alterations for a 21- $\beta$ -hydroxylase deficiency.

Blood tests	Results	Reference values
17-beta-estradiol	29.4 pg/ml	25-100 pg/ml
Progesterone	0.50 ng/ml	0.1-1.2 ng/ml
Testosterone	0.58 ng/ml	0.1-1 ng/ml
DHEA-S	122.2 $\mu$ g/dl	120-360 $\mu$ g/dl
17-OH-progesterone	1.40 ng/ml	0.40-1.02 ng/ml
$\phi$ -4-androstenedione	1.46 ng/ml	0.46-3.39 ng/ml
Cortisol	24 $\mu$ g/dl	5.6-23.1 $\mu$ g/dl
ACTH	48.2 pg/ml	10-60 pg/ml
LH	4.1 mIU/ml	0.7-19.4 mIU/ml
FSH	10.9 mIU/ml	2-12 mIU/ml
17-OH-progesterone (Synacthen)	0' 0.95, 30' 1.84, 60' 1.98 ng/ml	0.40-1.02 ng/ml

Discarded the possibility of a 21- $\beta$ -hydroxylase deficiency a mere medical treatment was unsatisfactory, so instrumental tests were performed to clarify patient's anatomy in view of surgery. Transvaginal ultrasound showed normal uterus characteristics. Ovaries had a normal echotexture; vagina was in a normal range for the upper two thirds, while in the lower third of its course had a junction with the urethra. Urography showed good concentration and elimination of contrast, normal bladder neck, but two urethral substenosis. At the end of urination, a vaginal opacification was evident, this showing continuity between vagina and urethra (Fig. 2). Subsequent MRI reinforced diagnostic suspicion showing a fusion between distal third of the urethra and lower third of vagina. At the confluence between the two structures MRI shows prostatic tissue.

### Surgical technique

The patient was subjected to antibiotic therapy and antithrombotic treatment with the use of elastic compression stockings. She underwent general anesthesia and placed in gynecological position on the operating table. The bladder catheter was placed through the urethral-vaginal common ostium (Fig. 3). A longitudinal incision of 2 cm was performed between the anus and the common orifice. A blunt dissection was made until the last third of the vagina and cervix. The last part of the vagina appeared structurally normal and covered by a normal vaginal mucosa. Subsequently on the anterior superior side of the neo-vagina urethral-vaginal fistula was detected. After identifying the urethral orifice a plastic was performed using the catheter as a guide to ensure patency of the urethra and the definitive separation of urinary tract from the genital one.



Fig. 3: Intra-operative evidence of urethra-vaginal fistula.



Fig. 4: An intra-operative step: crescent incision of clitoris.

During the same operation, the patient underwent a clitoroplasty. A crescent incision was made in the posterior portion of the clitoris (Fig. 4). The neurovascular bundle was isolated from the corpora cavernosa, that were excised. The glans was anchored to the symphysis pubis periosteum. The glans was not reduced in order to maintain sensitivity. At the end of surgery intravaginal prosthesis was placed covered with hyaluronic dressing gauze and antibiotic ointment. The patient was medicated three times a week for one month. After surgical treatment the patient was submitted to a test for assessing the sensitivity of the clitoris: Genito Sensory Analyzer (GSA). This test provides quantitative measurements of the sensitivity of the skin areas studied. This diagnostic tool allows us to investigate the neurological pathways responsible for the vibration and thermal sensitivity (hot-cold). The GSA test showed that both thermal and vibratile sensitivity were altered. This led us to re-plan the surgical procedure and program the patient to further clitoroplasty with reduction of the glans. The surgery was performed to ensure an optimal aesthetic result and a greater patient's satisfaction (Fig. 5).



Fig. 5: External genitalia aspect after two clitoroplasty.

## Discussion

A univocal inclusion in a classification for this malformation was not easy. Patient anomaly was part of the spectrum of diseases called disorders of sex development (DSD) <sup>1</sup>. Patient's anatomical features: clitoromegaly, fusion of the urethral and vaginal tract might seem to suggest a 21- $\beta$ -hydroxylase deficiency <sup>2</sup>. Hormonal tests the patient underwent to, allowed, however, to exclude abnormalities in hormonal cascade. Negativity to hormonal tests authorized us to approach the disease as a congenital malformation due to an abnormality of intrauterine development.

This kind of anomaly is undoubtedly the result of a defect into the embryologic development of the lower urogenital tract, but the mechanism is uncertain and may not be the same in all patients <sup>7</sup>. The separation of urinary and genital tracts in the normal female involves more than simply a lack of virilization; it also requires vacuolization of the vaginal plate and a caudal movement of the vaginal opening <sup>3</sup>. Because of the presence of a vaginourethral communication, it is tempting to speculate that the anomaly represents a rare form of persistence of the primitive urogenital sinus, coincident with either failure of distal migration of the primitive vaginal plate or failure of development or canalization of the distal vagina, all without virilization of the fetus. The cause of the changes is unknown.

It's considerable to emphasize that the association between clitoromegaly and the presence of a fusion of the lower third of the urethra with the vagina has not been previously reported in the literature.

According to Zdravkovic D et al. <sup>8</sup> in a cohort of 38 newborns with ambiguous genitalia the most common cause was 21- $\beta$ -hydroxylase deficiency (90%). This deficiency, however, was not present in the patient. In fact, 17-OH progesterone value is appropriate to a follicular phase and not elevated above the 8 ng/ml as in 21- $\beta$ -hydroxylase deficiency.

Another, more plausible diagnosis, could be represented by an idiopathic female pseudohermaphroditism <sup>9</sup>. The disease is due to the presence in the maternal circulation of large doses of androgens derived from an ovarian cancer or drug intake <sup>3</sup>.

Considering the last as the most probable diagnosis an initial medical treatment with steroids was performed, but the patient had not good results <sup>10,11</sup>. Surgical treatment was, then, carried out and should be considered the gold standard for this type of malformations <sup>6</sup>. The challenge mainly lies in the choice of treatment of the malformation and the absence of specific guidelines. The planning and timing of intervention was modified for functional and then aesthetic outcomes.

It is important, however, to especially emphasize two points, the reproductive and the psychological aspect strongly linked to the first one. As the girl did not show other anatomical or hormonal abnormalities the mere

absence of a vaginal orifice prevented a full sex life and the breeding. The reconstruction of an external vaginal meatus will allow the young girl to take wing with her normal life as a woman. The presence of the external genitalia with female characteristics allows the patient to restore a clear gender identity. These psychological changes need a long period to explicit; in the other hand changes related to the self-confidence were clear few days after surgery. While the patient was shy, detached and very shameful before surgery, subsequently appeared more sociable, even willing to learn the words necessary for communication in our language.

So in light of the difficulties encountered, of the wrong diagnosis made in another department, of the absence of a single etiology and the lack of specific guidelines for diagnosis of this disease, we propose a diagnostic algorithm. The target of this algorithm is to reach a diagnosis as early as possible in this border-line conditions.

The first step is a thorough history and physical examination designed to collect as much clinical evidence to direct toward a specific malformation pattern and it is also essential to assess the possible concurrence of other malformations. In the presence of a sexual ambiguity the first analysis to be made is the karyotype. Then it is important to perform routine blood tests and sex hormones values. The third step is imaging examinations, starting by ultrasonography, less invasive test that allows us to make a first evaluation of the genito-urinary district, then voiding cystography and retrograde urography. MRI / CT have to be performed in presence of additional questions and in pre-operative routine. A deep knowledge of the modified anatomy guides to a best surgical approach and is therefore essential. After diagnostic tests the patient underwent surgery. After surgery is significant to make sure that no iatrogenic alterations of the urinary tract have developed.

In conclusion it's important to highlight how a logical and clear approach to malformation problems can simplify treatment and give back to the little patient a normal relation life and a better self confidence.

## Riassunto

Lo pseudoermafroditismo idiopatico femminile è una patologia di raro riscontro dovuta ad alterazioni della produzione di androgeni durante la gravidanza da parte della madre. Questo difetto ormonale comporta un quadro fenotipico sovrapponibile ad una sindrome adrenogenitale. Descriviamo una malformazione con caratteristiche uniche in cui all'ipertrofia del clitoride, tipica della sindrome adrenogenitale, si associa l'assenza del meato vaginale e la fusione di questa con in terzo inferiore dell'uretra, e la tecnica utilizzata per un'efficace correzione chirurgica.

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