

# Leydig Cell Hypoplasia and Pituitary Stalk Agenesis: Genetic Link or Coincidence

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## Abstract

Leydig cell hypoplasia illustrates a rare category of 46, XY DSD "disorders of sex development". We report a case of a patient assigned to the female sex carrying a DSD with 46 XY karyotype on Leydig cell hypoplasia associated with pituitary stalk agenesis. This association has not been described yet in the literature. The patient was first admitted at the age of five for failure to thrive (FTT) with an abnormality of sexual development. The FTT was related to complete GH deficiency on pituitary stalk agenesis. Upon investigation, the patient was diagnosed as carrying a DSD 46, XY. The endocrine evaluation revealed low testosterone, FSH, and LH levels with a negative HCG test. The abdominopelvic ultrasound objectified two testicles in the inguinal folds. After discussing the case in a multidisciplinary consultation meeting, and taking into account the wishes of the family and the psychiatric expertise, the selected sex that was assigned to the patient was female. At the age of 19, the patient underwent a bilateral gonadectomy and the anatomopathological examination confirmed the diagnosis of Leydig cell hypoplasia. Leydig cell hypoplasia is a rare autosomal recessive syndrome, diagnosed by clinical, biological, radiological, histological, and genetic evidence. Its association with pituitary stalk agenesis has not been described in the literature. This syndrome is characterized by the inability of the chorionic gonadotropin luteinizing hormone receptor in Leydig cells to respond to luteinizing hormone, thereby causing feminization of a male fetus. The treatment has three components: hormonal treatment, surgical treatment, and psychological care.

**Keywords:** Leydig cell hypoplasia, 46 XY disorders of sex development, pituitary stalk agenesis, failure to thrive.

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## INTRODUCTION

Disorders of sex development (DSD) in 46, XY patients cover a broad spectrum of clinical patterns (female phenotype, posterior hypospadias, cryptorchidism). It is a defect in the development of the genitals of a child of XY sex due to an abnormality of the genes involved in the sex determination [1]. The diagnosis is based on careful clinical examination, hormonal assessment, molecular analyses, and sometimes surgical exploration with biopsy.

The causes are varied and affect the testicular determination steps (gonadal dysgenesis) or defects in the production or the action of testosterone (testosterone secretion abnormalities, androgen insensitivity, 5-reductase deficiency). Leydig cell agenesis illustrates a rare category of 46, XY DSD, resulting from the inability of the luteinizing hormone receptor gonadotropin chorionic (LHCGR) in Leydig cells to

respond to circulating luteinizing hormone (LH), thus causing a complete or incomplete feminization of a male fetus [2]. Its association with pituitary stalk agenesis has not been described in the literature.

DSD is one of the biggest challenges for urologists, endocrinologists, geneticists, and psychologists. The medical investigation should be carried out in the neonatal period, and it is necessary to only declare the sex of the child after further tests are conducted. Such a diagnosis requires caution in the way it is delivered to the parents because of the inevitable emotional consequences on the child.

We report a rare case of a patient assigned to the female sex carrying a DSD with 46 XY karyotype on Leydig cell hypoplasia associated with pituitary stalk agenesis.

## OBSERVATION

This is a 19 year old patient, she was born on 02/07/2000, of a third-degree consanguineous marriage, and was assigned to the female sex. She is the second of three siblings. In her medical history, the pregnancy was carried out to term, with a vaginal delivery without a notion of neonatal suffering, birth weight and height were normal, no disorders of sex development were reported in the family. Combined estrogen-progesterone pills were taken by the mother during the first trimester of pregnancy. At the age of five, the patient was hospitalized in our department for failure to thrive (FTT). The physical examination found a weight more than - 3 standard deviation (SD) and a height more than - 4 SD below the mean with signs of somatotrophic insufficiency (babyface, rounded forehead with saddle nose), the examination of external genitals revealed a scrotal-like labia majora with transverse folds, a 1.5 cm genital tubercle (GT) with one orifice at its base. The palpation found two gonads at the inguinal folds.

FTT exploration found a delayed bone age by 4 years, low levels of IGF1 and FT4, and complete GH deficiency. Hypothalamic-pituitary MRI objectified pituitary stalk agenesis.

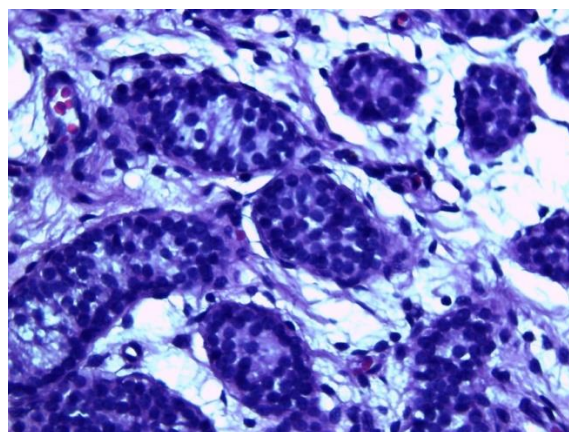
Regarding the investigation of the sexual abnormality, the chromosomal analysis found a 46 XY karyotype. Endocrine exploration revealed a normal

level of 17 hydroxyprogesterone, androstenedione (Delta4), and dehydroepiandrosterone sulfate (DHEA-S), thus excluding an enzyme block. Testosterone levels were low with a negative testicular stimulation test with chorionic gonadotropic hormone (HCG). The FSH, LH, and estradiol were low (Table 1).

The abdominopelvic ultrasound objectified two testicles in the inguinal folds with no uterine or ovarian formation. Genitography showed a long male-type urethra and revealed the absence of paramesonephric ducts. To treat the FTT, the patient was put on growth hormone therapy and Levothyroxine. After discussing the case in a multidisciplinary consultation meeting and taking into consideration the wishes of the patient and her parents, as well as the psychiatric assessment, the selected sex was female. It was decided to wait until puberty to schedule a gonadectomy. At the age of 19, the patient underwent bilateral gonadectomy, and the anatomopathological examination was in favor of infantile testicular gonads with the absence of Leydig cells (Figure 1). The patient was put on estrogen replacement therapy and the feminizing genitoplasty is planned. After fourteen years of follow up, the clinical evolution under growth hormone and estrogen replacement therapy was marked by reaching a height of 168 cm and pubertal development estimated at stage III according to Tanner staging.

**Table 1: Hormonal assessment of the patient at the age of 5 & 14**

	5 years old	14 years old
TNE	0,17ng/ml	<0,025ng/ml
FSH	0,5mU/ml (0.2-2.8)	1,2UI/l(1,5-12,4)
LH	<0,2mU /ml (<0,1-1,3)	0,6 UI/l(1,5-8,6)
E2	< 5 pg /ml (<0,5-20)	
PNE	0,061 ng/ml	
SDHEA	<6 µg/ dl	0,5ng/ml(1,2-18,9)
17 OH PNE		0,8 nmol/l
17 OH PREG		0,2ng/ml(0,3-1,9)
ANDROSTENDIONE	0,5 nmol/l (<1)	0,7nmol/l(0.7-5,2)
DHT	-	0,08ng/ml(<0,05)
T/DHT	-	0,31
HCG test	TNE=0,11ng/ml	



**Figure 1: Histological section confirming LCA**

## DISCUSSION

In our case, the clinical presentation, as well as the biological and morphological data, are in favor of sexual differentiation disorder 46, XY related to Leydig cell agenesis. The diagnosis was confirmed by the anatomopathological examination. To our knowledge, our case is the first one to report the association of LCH with pituitary stalk agenesis. This association may be the result of an underlying genetic disorder that has not been described yet. Further studies are required to determine whether the association is indeed due to a genetic link or if it is the case of mere coincidence.

In 1976, the first patients with LCH were recorded and other cases followed. It is a rare autosomal recessive genetic syndrome affecting approximately 1 in 1,000,000 individuals. Also known as Leydig cell agenesis, it is characterized by an inability of the body to respond to LH, which is normally responsible for signaling Leydig cells. These cells do not differentiate normally and do not secrete testosterone. Thus, affected male infants are born with ambiguous genitalia, or with external genital organs of female appearance. Paramesonephric ducts are absent due to unaffected secretion of AMH by Sertoli cells. The LCH has been classified into two subtypes based on clinical gravity. The first type is external genitals that are not entirely female with undescended testicles as described in our case, while the second category is related to a relatively mild phenotype which can include micropenis, hypospadias, and cryptorchidism [2].

The diagnosis of type 1 LCH can be made during the neonatal period. However, it is often done later as reported in our case. Jahan *et al* reported the case of a patient who had 46, XY DSD due to Leydig cell agenesis: the diagnosis was not established until the patient was 27 years old and presented with primary amenorrhea [2]. This underlines the importance of a careful clinical examination at birth, allowing early and appropriate care defining the sexual assignment of the child [3]. The description of anomalies must be as precise as possible. Likewise, it is essential to make sure to use neutral vocabulary, adapted to the situation, especially in the presence of the parents, by using sexually “homogenous” words: genital tubercle (for penis or clitoris), genital folds (for labia majora or scrotum) and gonads (for ovaries or testicles).

The typical biochemical profile of patients with LCH includes elevated levels of LH (and FSH) in early infancy or during puberty. In our case, FSH and LH levels were low due to the pituitary stalk agenesis. In childhood, when the GnRH (Gonadotropin-Releasing Hormone) pulse generator is inactive, basal LH levels can sometimes be detected above the normal range. Plasma levels of 17-OHP, androstenedione, and testosterone are low, with little or no response to prolonged stimulation with HCG [4]. Consanguinity was noted in the case reported by Schwartz *et al.*, [5].

Consanguinity in several other families (e.g. El-Awady *et al.*, Kremer *et al*, and Laue *et al.*, [2, 6] supported autosomal recessive inheritance. LCH is caused by genetic mutations in the LHCGR gene that encodes the LHCGR protein [2]. The LHCGR gene is mapped on chromosome 2p21. The 674 amino acid protein is a receptor coupled to the G protein of the transmembrane domain 7. The underlying gene defect in LCH was first described by Kremer *et al* and various other defects have since been described [2]. More than 20 mutations have been reported in the receptor gene (LHCGR) resulting in decreased reactivity to hCG and LH, which causes Leydig cell agenesis [2]. In our case, the diagnosis of the 46, XY DSD on LCH was based on the histological data (Figure 1). The genetic study was not carried out as it is not available in Morocco.

The decision about the sex of patients with abnormality of sexual development requires simultaneous and precise assessment of the psychological dimension [7]. Money *et al* studied 172 cases related to the abnormality of sexual development, in which 39 cases are 46, XY DSD. For these patients, psychosexual orientation does not depend on their genetic sex or their gonadal sex, but it is essentially linked to the family atmosphere and especially to education. The treatment of patients with type 1 LCH involves bilateral orchidectomy, vaginal dilation, and hormone replacement (estrogen) to initiate the development of secondary sexual characteristics and puberty. Our patient was assigned to female sex at birth. Afterwards, considering the desire of the patient, the psychiatrist expertise and the family, in addition to the social and familial environment, the sex selected was female. It was decided to wait until puberty to schedule a gonadectomy. She is now surged and followed by our endocrine department and decided to stop psychotherapy as she feels well. No study could provide recommendations on the age at which gonadectomy should be performed. Indeed, some authors adopt a safer approach and wait until adulthood to decide on the surgical procedure.

## CONCLUSION

LCH is a rare autosomal recessive syndrome, diagnosed by clinical, biological, radiological, histological, and genetic evidence. The treatment has three components: hormonal treatment, surgical treatment, and psychological care. Multidisciplinary care is essential to avoid errors and diagnostic delay. The sex of the newborn should be carefully chosen, considering the possibilities of virilization, fertility, the complexity of the reconstructive surgery, and the patient's anticipated self-image. The particularity of our case is the association of LCH with pituitary stalk agenesis, which masks the increase of LH that is usually found in LCH at the time of puberty.

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