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A 46 XY DSD Revealed by Puberty Delay, when a Tree Hides the Forest

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Abstract **Case Report**

DSD 46 XY constitute an entity of sexual differentiation disorders well codified semantically, but very heterogeneous clinically and etiologically. These are several conditions of varying severity, but all characterized by a male chromosomal sex, attested by genetic identification of gonosome Y, and associated with either gonad dysgenesis (testicle), or malformations of the male genital tract, ranging from a simple hypospadias to a typically female phenotype [1]. The etiological diagnosis of DSD is delicate, and it involves a clinical and biological evaluation at first, followed by molecular biology examinations. The nosological framework associating 46-XY DSD with a female phenotype implies the presence of completely dysgenetic gonads. Etiologies are dominated by mutations in SRY and SF1 [2]. Through this work, we describe the case of a young «girl» of indisputable female morphotype, and in whom the diagnosis of a 46 XY DSD was established before pubertal delay and primary amenorrhea. ***Objective:*** always consider the diagnosis of DSD regardless of the age of the patient, and establish an etiological diagnosis according to the means available. ***Ethical considerations:*** In accordance with current regulations, an informed, written and verbal consent was provided to the guardians of the young patient before considering the publication of this work.

Keywords: 46-DSD XY _ Dysgenetic gonads _ Cytogenetics.

INTRODUCTION

Embryonic development is a crucial and determining stage in the life of all living beings of the animal kingdom, especially in mammals, including the human species. Therefore, any anomaly altering the organogenesis will have irreversible repercussions on one or more vital, functional and/ or aesthetic functions of the affected individual. In humans, sexual differentiation is one of the most studied functions in embryology. These are very complex cascades of differentiation and development, involving dozens of genes and transcription factors. The first draft of gonad appears around the 5th Development Week, in the form of a simple urogenital ridge. This rudimentary draft initially engages in the formation of a so-called bi-potential gonad. A process that can only take place in the presence of factors such as SF1, LHX9 and WT1 also have a considerable effect in this process. In a second step, the gonad takes one of the specific male or female differentiation pathways under the influence of specific factors, the most important of which is the SRY carried on the Y chromosome [3]. In the absence of male-type factors, spontaneous differentiation into female gonads is the rule (process also supported by a set of transcription factors). The gonads, once gender-specific, begin to secrete sex steroids which, in large quantities and acting on functional receptors, will orchestrate the complement of the organogenesis of the genital tract. The antimüllerian hormone AMH which is the main hormone in the balance of the protagonists Muller channels/ Wolf channels, the 5 alpha-reductase, as well as the receptors to these 2 hormones play an indisputable role in the sculpture of the definitive sexual character [3].

DSD sexual development disorders constitute a rare and heterogeneous group of pathologies. They are characterized by a discrepancy between one of the sex determinants in the same individual: between the chromosome, gonadal and/or anatomical entity [1]. The term "developmental disorders" was introduced since the 2006 consensus, with a view to putting an end to pejorative connotations related to the old nomenclature such as "pseudohermaphroditism" or "sexual ambiguity" [1]. Other authors currently tend to use the term "differences" instead of "disorders" for the same reason [2, 4, 5]. This entity of congenital pathologies often poses problems of etiological diagnosis, resulting in the prescription of a considerable number of molecular genetic examinations. However, access to genetic

diagnosis is often reduced in most countries of the world. We report in this work the case of a female morphotype child, living with DSD type 46 XY, of late discovery at the peripubertal phase.

OBSERVATION

This is a young girl of 16 years, high school student with a good academic performance, and the eldest of 2 siblings. Accompanied by her tutor, «She» was referred to us by the family doctor for pubertal delay and statural delay. This child is from a non-insulated marriage. In her history there was no intake of toxins by the mother during pregnancy, nor any particular pill or chemotherapy. And no pathology was recorded in neonatal life; especially no loss of salt. At the time of his birth 16 years ago, the diagnosis of fetal sex was easily made in the delivery room and was announced to the family as being «female sex» in front of external genitalia typically of female type. Our current examination finds a female morphotype; female external genitalia, infantile seen an aspect of the anterior vulva and dry. Showing no signs of virilization, particularly without clitoral hypertrophy (see image 1). Breast development is infantile. Tanner's stage was B1 H2 (breast 1, hair 2). It is 157cm in size (-3DS with respect to age) and -2 DS with respect to the target size, without dysmorphic syndrome except a low implantation of the hair. The assessment of cognitive functions was good, without any stigma of mental retardation.

Biologically, a profile of hypergonadotropic hypogonadism, Estradiol=20.3 pg/mL FSH=69.9 mUI/mL and LH=12.6 mUI/mL is objective. Collapsed AMH<0.01 and Inhibin B. Total Testosterone was a female value of 0.14 ng/mL. Cortisol, hypophysiogram and thyroidal function returned without particularity. The karyotype that we asked for for a suspicion of Turner syndrome, had returned - against all odds - a 46 XY (see image 2)! A second confirmation was considered coupled with a FISH, in order to eliminate a possible technical wandering, had affirmed the caryotype 46 XY without chromosme Y deletion anomalies and without trace of a cross-over. Our. For the somatotropic axis, IGF-1=225 ng/mL (N: 122-524), base GH=0.1 mUI/L. Bone age was delayed: 11 years and 06 months. We conducted a combined GH stimulation test using glucagon-Propanolol, the result of which did not reveal somatotropic deficit; the GH under test had reached a maximum of 58.24 m-IU/L at time T150 and 39 m-IU/L at time T180.

Pelvic imaging, ultrasound and MRI examinations found a vulva and vaginal cavity of normal signal, the uterus mesuring 60* 24 mm at normal signal myometrium and with a cavity area of 9mm hypersignal T2, without visible gonads or annexal formation. After multidisciplinary consultation meeting, we proposed a genitography, back in favor of a vaginal cavity of normal size and depth without image of tubes. Followed by diagnostic and interventional laparoscopy. Laparoscopy found drafts of dysreproductive gonads in the form of thin and pale strips, biopsies made initially and extemporaneous examination, followed by their resection for Anatomopathological examination. After a child psychiatry interview and informed parental consent, we decided to continue the process of feminization. Our young patient did not have gender dysphoria according to the history of child psychiatry and she defines herself as a girl. The psychological management of the patient has been integrated into our management in order to overcome the transition phase, and to provide support with regard to the major issues raised by the diagnosis; particularly the question of fertility and quality of life. Our etiological diagnosis was limited to the clinical-biological stage and the search for deletions of the Y gene on karyotype. While the sequencing of the SRY, SOX9 and SF1 genes was proposed to the family but not carried out for lack of means. Our subsequent therapeutic management consisted of hormone replacement therapy, first ostrogenic and then combined with estradiol ethinyl and dydrogesterone.

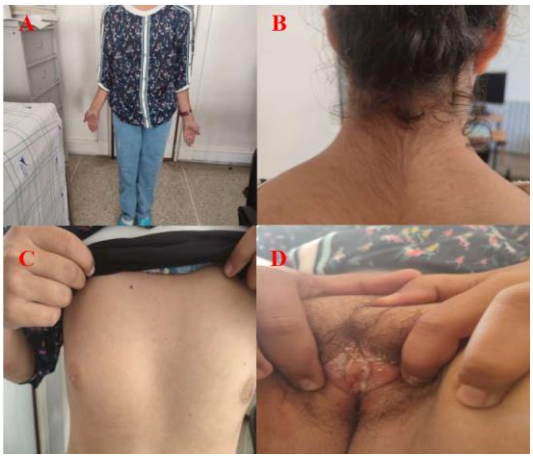

Image 1: A: Absence of clinical dysmorphia. B: Low hairline. C: Childish breasts S1. D: Normal-appearing vulva with pubic hair P2

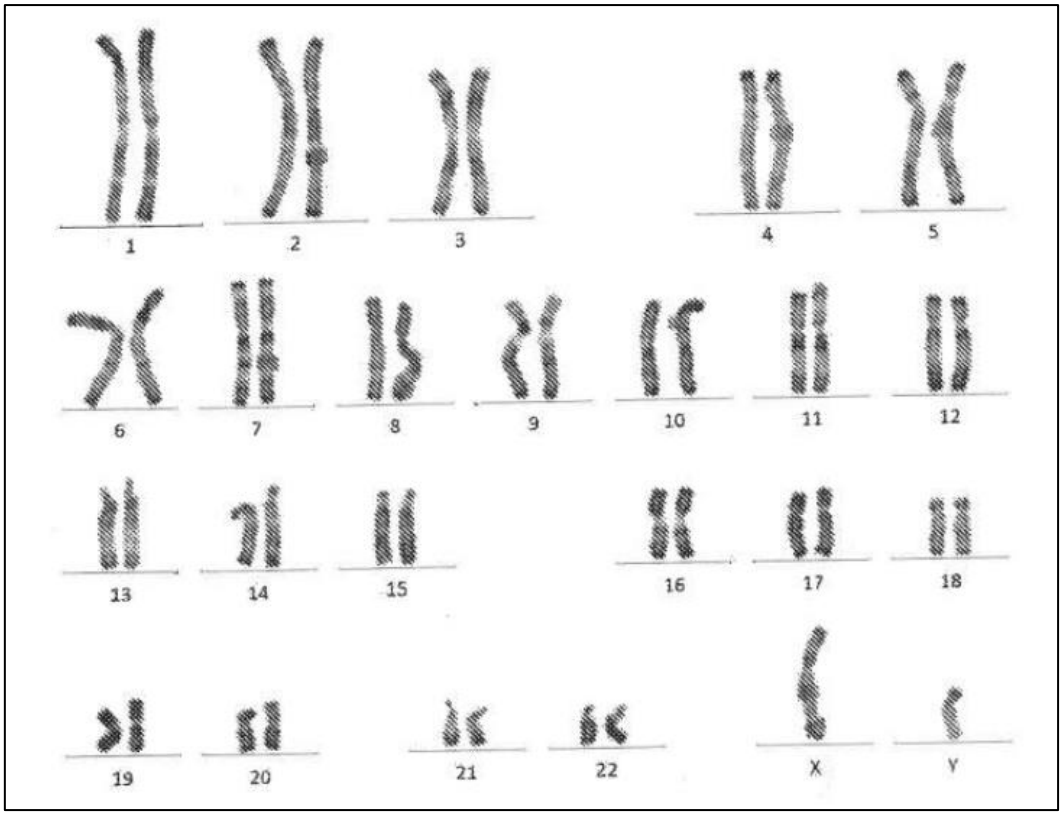

Image 2: Karyotype showing a 46 XY in the case we report

DISCUSSION

The prevalence of DSD is difficult to estimate in the general population. This is due to their clinical and etiological heterogeneity, but also to several societal constraints making this disease a taboo subject in many countries around the world. The absence of a national register dedicated to the identification and monitoring of DSDs in our context tends to make the task even more difficult, on the one hand, to estimate the real incidence of these diseases and on the other, to issue a local consensus to better deal with them. In a 20-year retrospective study in Switzerland, the number of DSD cases recorded had reached 561 cases. 32% of the population had 46 XY DSD, while half of the cases had chromosomal aberrations as a source of DSD [6].

The classification of DSDs is currently based on the mechanism involved in their genesis rather than their clinical expression [1]. There are four distinct groups:

- First group: includes malformative abnormalities of the urogenital system, and divided into malformations of the male urogenitals sinus (isolated hypospadias, and aphalia), and the female tract (Mayer Rokitansky-küster-hauser syndrome as an example).
- Second group: consisted of abnormalities of differentiation of the gonades. They are of chromosomal origin, either through aneuploids, rearrangements, supernumerary chromozomes or ultimately secondary to punctual mutations on the genes encoding the transcription factors. This large group can itself contain 4 subgroups depending on the degree of dysgenesis (complete, partial, moderate and mosaic). Turner's and Klinefeleter's syndromes are found in this group.
- The third group: whose physiopathological origin is purely endocrine, groups together all forms of congenital adrenal hyperplasia. These abnormalities can lead either to virilization of a fetus 46,XX or to a lack of synthesis or action of androgenes leading to a feminization of the foetus 46,XY.
- The fourth group is that of the rest of the undefined forms.

In a Brazilian cohort of 209 cases of 46 XY DSD, the contributions of molecular biology were undeniable in redressing the etiological diagnosis. In fact, the molecular diagnosis was obtained in 59.3% of cases, leading to improvement in the diagnosis of causality which went up to 78.9% of all patients diagnosed, using clinical, biochemical and molecultural methods all confused [8]. In the case of our patient, the initial nosological framework is a DSD syndrome with a genotype 46 XY, and phenotypically external female genital organs, combining very large mullerian residue (uterus and cervix), but without gonades. The present situation suggests a differentiation anomaly that appeared very early and led to a complete gonadic dysgenesis, an element confirmed by the anatomopathological examination of the resecrated

annex vestige. Furthermore, the resection of the Mullerian residues found in our patient was the subject of a multidisciplinary meeting, and was justified by the risk of carcination of these residue, a risk by several authors [7]. Indeed, the etiological diagnosis in this specific framework involves an etiological research plan that cannot be completely calculated on the above-mentioned classification, because the causes may belong either to group 3 (pure and complete gonadic dysgenesis), or to group 4 involving a very early anomaly of the LH and/or AMH signaling [2]. Other genetic abnormalities, such as the AR mutation and CBX2 [9], cannot be excluded, while the anomalies in the production and/or action of androgenes would have given a rather mild picture, and in principle without mullerian residues [2, 14].

- SRY mutations: The SRY gene carried on the Y chromosome is the key to male sexual differentiation. This gene holds its place after the work of Koopman and Al. Having demonstrated testicular development in a female mouse cloned with this gene [11]. It is a gene belonging to the family of SOX genes and endowed with a molecular function enhanced by the HMG complex (high mobility group box), thus acting as a powerful transcription factor [10]. The resulting mutations are the result of rearrangements of type SOX3 (Xq27.1), SOX9 (17q24.3) and SOX10 (22q13.1) [20]. The link between mutations of the HMG-box complex and DSD with complete gonadic dysgenesis has been established since 1994 [12]. While The identified mutations are multiple and often de novo [13].
- DAX1 and SF1 mutations:
  DAX1 (recently recognized as NR0B1) and SF1 (Steroidogenic factor-1) are two nuclear transcription factors. They are expressed in the fetal adrenal and gonadotropic axis and would therefore be involved in the differentiation of both the adrenals and the gonads [15]. The DAX1 mutation intervenes by inhibiting SF-1 and can often lead to forms leading to ovotestis [17]. Therefore, DSDs associated with SF1 mutations can also be accompanied by adrenal insufficiency, as demonstrated by several authors. [16]
- WT1 mutations:
  Like the SRY, the WT1 gene also cloned for the first time in 1990 [21], it is an essential factor in the genital differentiation but also urological especially kidney. In addition to the DSDs, its mutation may lead to chronic diseases [18]. Mutations at the level of the WT1 gene are often de novo and cover the entire gene including the introns [19].the clinical expression of the resulting mutations is unpredictable and may give different pictures [21].
- The AMH and Rc AMH mutations:
  According to several authors, AMH dosage is therefore indispensable in the case of DSD [22]. However, the absence of AMH in the serum of an index subject does not completely rule out the lack of germinal cells, as it does not allow for a reliable diagnosis of a DSD [24]. In our young patient, AMH and B inhibitor levels were undetectable. This allowed us to suggest, on the one hand, the presence of a complete gonadic dysgenesis (affirmed later after celloscopy), and on the other hand to offer an explanation to the estrogen level observed at 20.3 pg/mL, excluding any ovarian source of these estrogens, thus allowing to retain an adrenal source through an aromatization process. In fact, AMH is secreted by Sertoli cells and binds to its type 2 receptor and acts by blocking the development of Muller structures. Mutations in AMH or its receptor cause 46 XY DSD with female tract persistence at varying degrees [23].
- Other mutations and other factors:
  Androgen insensitivity AIS (or androgen resistance) syndrome and 5-alpha-reductase deficiency are classic and common causes of 46 XY DSD. Easy diagnosis based on T/DHT ratio <20 preferably in stimulation in a XY peripuberal individual [26]. CBX2 is an epigenetic regulator, acting as a chromatin modulator. CBX2 mutations are related to 46 XY DSD in several cases in the literature [25]. Other spot mutations have been attributed to DSD type 46 XY such as DMRT1, NR5A1, DHH, DHX37) [27].

CONCLUSION

The repercussions of sexual differentiation disorders are multiple and are not limited to organic malformations. This involves multidisciplinary care, integrating medical psychology as a pillar in the decision-making of a sexual reorientation as well as in the long-term follow-up. Gender dysphoria is one of the concerns for clinicians dealing with this type of pathology, and the treatment of which is not yet clarified [28]. After a positive diagnosis of a form of DSD, the first evaluation is crucial and includes a good biological and imaging clinical study. The data obtained through this first evaluation form the solid basis on which genetic examinations will be based.

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