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Abnormality of 46XY sexual différentiation: About 30 cases

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Abstract: *A retrospective study of 30 patients with sexual differentiation 46XY abnormality collected over 19 years to assess the clinical and etiological characteristics. The disease is rare; the age at diagnosis is in generally late at 8.5 years (02 months - 25 years). However the defect is found at birth in most cases (82.5%). In half of the cases, the first Endocrinology consultation is done between the second and the sixth year. Sexual ambiguity is severe in 10% of cases. We discerned three predominant etiologies: the androgen resistance (26.6%) gonadal dysgenesis (20%) and the enzyme block (20%). In nearly a third (26.6%) no etiology was found.*

Keywords*: Sexual differentiation, Quigley classification, androgen resistance, enzymatic block, gonadal dysgenesis, sexual ambiguity.*

I. Introduction

The anomalies of sexual differentiation (ASD) 46XY represent a serious birth defect observed in the newborn. It corresponds to a failure of masculinization in external genitalia of a fetus with 46 XY genotype or a 46XY / 45X0 mosaics.[1] Such cases report an anomaly of testicular determination, a disorder in hormone synthesis of testosterone or androgen resistance. Whatever the pathogenesis, ASD shares a polymorphic clinical spectrum that goes from complete female phenotype to a male phenotype making its diagnosis and treatment difficult.[2] The objective of this study is to report the clinical and etiological features of patients with 46XY ASD.

II. Materials and Methods

30 patients with 46 XY ASD were hospitalized between 1996 and 2015. All patients received in addition to questioning and a thorough clinical examination, a para- clinical exploration which was as complete as possible.Hormonal assay was carried out with balance of plasma testosterone at baseline and after testicular stimulation test by HCG (1500 IU on alternate days for a week), dosage of FSH and LH in plasma, assay of AMH, of adrenal androgen precursors after synacthen and HCG tests and measurement of plasma ACTH. In cases of suspected disorders of the adrenal the adrenal hormonal synthesis, also a study of peripheral androgen responsiveness assessed by the increase in the size of the penis after administration of testosterone was done.
A radiological assessment with pelvic and genital ultrasound and a cytogenetic study with BARR test and karyotype from peripheral blood completed the examination. In all cases a psychological evaluation was performed in all patients and parents before the therapeutic decision.

III. Results

The average of age at diagnosis was in general late: 8.5 years (02 months - 25 years). The defect is found at birth in most cases (82.5%). In half of the cases (n = 15/30), the first endocrinology consultation took place between the second and the sixth year of life (table I). Table (I): Age of the patients at the first consultation in Endocrinology. The reasons for consultations were sexual ambiguity in three quarters of cases (76.6%). The latter was associated with dehydration in 10% of cases (table II).

Table (II): The motives of consultation for patients with TDS Parental consanguinity was observed in 37.5% of cases. In six cases there was a familial form. The declaration of the civil sex was mostly for males (82%). The sexual ambiguity was severe in four cases (Table III). Table (III): Distribution of patients according to the classification of Quigley. Almost all patients had a 46 XY karyotype. Two patients had a mosaic XY 46/45 X0. The etiologic survey found three predominant main causes: the androgen resistance (26.6%) gonadal dysgenesis (20%) and the enzyme block (20%). In nearly a third (26.6%) no etiology was found (Table IV).Table (IV): Distribution of patients according to the etiology.Therapeutically, surgery of hypospadias was long, difficult and incomplète in all patients. Androgen therapy indicated for four patients because of an important bud genital hypoplasia allowed the increase in the size of the penis.Three patients underwent castration because of severe ambiguity, as per the desire of parents at a later stage. An important psychological impact was observed in older series (n: 4, average age 14.5 years) and for all parents.

IV. Discussion

Despite early recognition at birth of the genital malformation the diagnostic and therapeutic management remains delayed in our country (8.5 years on average). This delay is due to the ignorance of the disease on the one hand and the lack of systematic examination of the external genitalia in newborns. The diagnosis is raised to a very late age, because the AS D remain a taboo subject, and nobody talks about it in our society. The diagnosis proves that difficult in most cases, because the treatment is expensive, the majority of patients have a low socioeconomic level and also because molecular biology is not developed in our country

A careful clinical examination is necessary to define the importance of sexual ambiguity and search for clinical elements that guide the etiological exploration such as the existence of family genital abnormalities in favor of an androgen resistance or an enzymatic block especially if there is a neonatal salt loss syndrome (figl) or the presence of a poly malformation context.[1] The medical management, both surgical and psychological of patients with ASD 46 XY and their families, is essential. Fast and efficient support is needed. It involves a rigorous process that should lead to etiologic diagnosis and the correct therapeutic choice. This approach must result from the experience of a multidisciplinary team consisting of pediatricians, endocrinologists, radiologists, surgeons, geneticists working together closely.[3] The initial exploration of an ASD should be done during the neonatal period. It must contain a baseline testosterone assay after a chorionic gonadotropin stimulation.[4]

The androgen sensitivity test is often necessary to define the sex orientation in severe forms. The karyotyping and the analysis of chromosome Y by TCR of the testicular determining gene are essential for the diagnosis of ASD. Precise analysis of genes involved in sex determination is necessary in accordance with the diagnostic orientation.[5] According to the literature, androgen resistance is the most common cause (fig2).[6] It should be noted that for more than a decade, considerable advances in genetics and molecular endocrinology have contributed to a finer dissection of the various stages of normal sexual differentiation. This is an essential basis for the identification and management of sexual ambiguities. However it should be noted that despite these advances, no etiology is found in half the cases.[7] Large deficiencies still exist in etiological explorations of sexual ambiguity in our country. The lack of means of examination complicates patient care that is thereby delayed. The development of technology particularly cytogenetic, is fundamental because it plays an important role in the etiological diagnosis of sexual ambiguity.Therapeutically, the choice of sex remains a difficult step and must take into account the age at diagnosis, genitalial anatomy and hormonal explorations. The therapeutic decision is difficult and must be based on an experienced multidisciplinary team.[5]Early diagnosis is important as it helps to reassure the families and improve the identification of children. It must be emphasized that results are better in génitoplasties feminizing than in génitoplasties masculinising. Masculinization surgery has seen too much progress over the years, but it remains a surgery that is difficult and borrowed by a considerable morbidity. The presence of testicular tissue is not the essential argument in the therapeutic decision, but surgical repair and the quality of testicular response to gonadotropin are critical elements for predicting pubertal development.Choosing the sex of a child with AS D needs to be done together with an accurate psychological assessment .Money and Hampson[8] studied 172 cases of developmental abnormalities sexual, of which 39 cases are 46, XY ASD. They concluded that the psychosexual orientation depends neither on their genetic sex or their gonadal sex, but it is linked mainly to family-friendly and especially to education factors. Wilkins[9] who studied 30 cases of sexual development abnormalities, concluded also that the important consideration in determining the sex is the "Gender role" which can simply be called "sexual behavior" (opposition to reproductive behavior). According to Wilkins, this sexual behavior is determined by the sex assigned at birth, education and whatever other determinants of sex:chromosomal, gonadal, hormonal, internal reproductive organs.

V. Conclusion

ASD is a serious birth defect that must be diagnosed and supported early. Genetic, hormonal and imaging studies have allowed clinicians to take better care of this condition. However choosing the sex is still difficult and a source of anxiety for parents and doctors. The experience of a multidisciplinary team is essential to the management of ASD.

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Figures

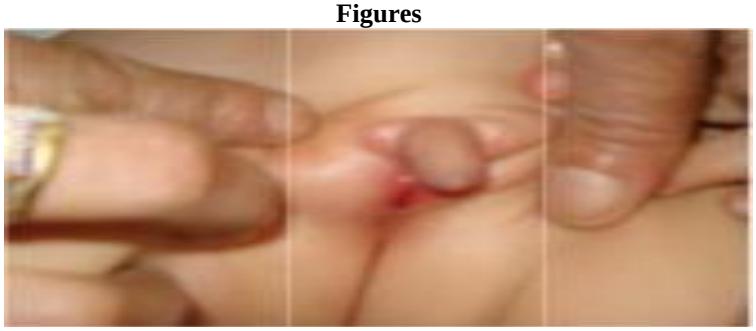
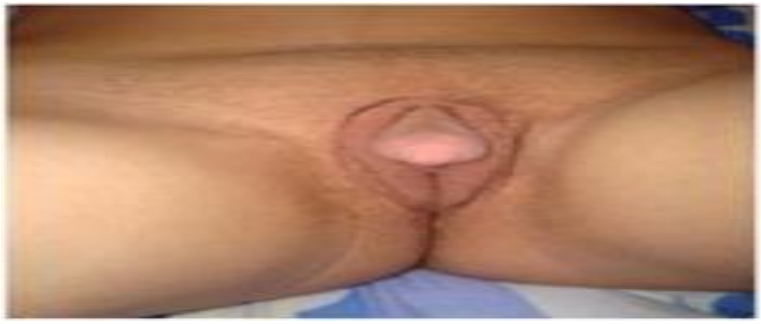


Fig1 : congénital adrenal hyperplasia



Tables

Table (I): Age of the patients at the first consultation in Endocrinology.

Years	Number of patients (%)
1st year	10 (33,3)
2nd and 6th years	15 (50)
After 13 years	5 (16,6)

Table (II): The motives of consultation for patients with TDS

Consultation purpose	Number of patients (%)
sexual ambiguity	20 (66,6)
cryptorchidism	4 (13,3)
Ambiguity and dehydration	3 (10)
primary amenorrhea	3 (10)

Table (III): Distribution of patients according to the classification of Quigley.

stage	Number of patients (%)
2	20 (66,6)
3	6 (20)
5	4 (13,3).

Table (IV): Distribution of patients according to the etiology.

Etiology	Number (%)
Androgen resistance	8 (26,6)
gonadal dysgenesis	6 (20)
Enzymatic block 3 3 ol Dehydrogenase	6 (20)
Poly malformation syndrome	2 (6,6)