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Review article

Surgery in disorders of sex development (DSD) with a gender issue: If (why), when, and how?

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Summary
Ten years after the consensus meeting on disorders of sex development (DSD), genital surgery continues to raise questions and criticisms concerning its indications, its technical aspects, timing and evaluation. This standpoint details each distinct situation and its possible management in 5 main groups of DSD patients with atypical genitalia: the 46,XX DSD group (congenital adrenal hyperplasia); the heterogeneous 46,XY DSD group (gonadal dysgenesis, disorders of steroidogenesis, target tissues impairments …); gonosomic mosaicisms (45,X/46,XY patients); ovo-testicular DSD; and "non-hormonal/non chromosomal" DSD. Questions are summarized for each DSD group with the support of literature and the feedback of several world experts.

Given the complexity and heterogeneity of presentation there is no consensus regarding the indications, the timing, the procedure nor the evaluation of outcome of DSD surgery. There are, however, some issues on which most experts would agree: 1) The need for identifying centres of expertise with a multidisciplinary approach; 2) A conservative management of the gonads in complete androgen insensitivity syndrome at least until puberty although some studies expressed concerns about the heightened tumour risk in this group; 3) To avoid vaginal dilatation in children after surgical reconstruction; 4) To keep asymptomatic mullerian remnants during childhood; 5) To remove confirmed streak gonads when Y material is present; 6) It is likely that 46,XY cloacal exstrophy, aphallia and severe micropenis would do best raised as male

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although this is based on limited outcome data. There is general acknowledgement among experts that timing, the choice of the individual and irreversibility of surgical procedures are sources of concerns. There is, however, little evidence provided regarding the impact of non-treated DSD during childhood for the individual development, the parents, society and the risk of stigmatization. The low level of evidence should lead to design collaborative prospective studies involving all parties and using consensual protocols of evaluation.

Introduction

Ten years after the Chicago consensus meeting [1], genital surgery continues to raise questions and criticisms concerning its indications, its timing, and its technical aspects [2,3]. Opinions are more common than facts as the volume of patients in each group of disorders of sex development (DSD) is small, management is extraordinarily heterogeneous across centers, and pre- and post-treatment evaluations are mostly subjective, examiner-dependent, and culturally influenced. Hence, the classical methodology of evidence-based medicine meets major hurdles, which are responsible for several unanswered questions that we attempt to list in this standpoint article.

The first major hurdle is the definition of the acronym DSD. Does it include all congenital developmental genito-sexual anomalies, and, if so, are undescended testicles, hypospadias, or even labial adhesions included? Or should the definition be limited to situations in which there is an inadequacy between genital anatomy (phenotype) and biological profile (biotype), which may raise questions about gender assignment? This restrictive definition of DSD does not identify genital anomalies with no detectable biological or chromosomal anomalies, which represent the vast majority of patients.

The second hurdle is semantic as the terms "gender," "sex," "sexual," have discordant interpretations. "Gender" is a social concept, which is the way the society mirrors the "individual identity." It does not take into account the "individual identity" ("inside identity") and the future "gender role" ("behavioral identity"), which are invisible at birth and the modalities of which are mostly unknown, that is multifactorial [4]. The term "genital" has been avoided in the Chicago meeting, although atypical genito-sexual development should be the main focus of this discussion. Hence, it is essential to correlate phenotype and biotype as atypical anatomy is the first clinical sign from which suspicion of a DSD is raised in the newborn and will lead to a chain of investigations to define to which group of DSD the patient belongs.

Who are we talking about? What difficulties are met in the management of each of the following DSD groups?

Using the Chicago canvas [5], five main groups of DSD patients may be identified, submitted to the gender assignment process, and may be considered for a surgical genital reconstruction.

(1) In the 46,XX DSD group, classical congenital adrenal hyperplasia (CAH) represents the most common diagnosis. There is usually no gender issue in this group, except in case of late diagnosis and severely masculinized 46,XX individuals. Genital phenotype of prenatally non-treated 46,XX CAH patients at birth includes an increased development of the genital tubercle (GT) along with an increased length of the urethra, the opening of which is usually located on the ventrum of the GT, although in the most severely masculinized cases it may constitute a normal-looking phallus [6]. These features are similar to those of a 46,XY hypospadiac GT with non-palpable testes. In 46,XX CAH, the vaginal cavity opens into the posterior wall of the urethra at a variable distance from the bladder neck but not higher than where the veru montanum (mullerian structure) is normally located in the male urethra. This confluence is also at variable distance from the perineum depending on the development of the urethra and the increased thickness of the pelvic floor muscles. The height of the urethro-vaginal confluence is not related to the degree of external masculinization, contrary to suggestions from the Prader classification [7,8]. The sagittal fusion of the genital folds is variable, from an almost feminine vulva to a complete scrotal-like appearance. In all cases, the gonads are not palpable in the genital folds. Recent evidence suggests that female classical CAH patients and caregivers do not wish to be considered to be DSD patients [9].

(2) The 46,XY DSD group is more heterogeneous, mostly including: abnormal androgen steroidogenesis, particularly 17β hydroxy steroid dehydrogenase (17β HSD) deficiency; and 5α reductase deficiency, which is more common in some areas in the world in which consanguinity is frequent (e.g. the Dominican Republic, New Guinea, and the Gaza strip). In these two first groups, the phenotype is often feminine at birth but will become virilized at puberty. The testicles are often palpable in the inguinal region. There are no mullerian structures as the AMH function remains intact. Internal genital organs are male.

These are two situations for which controversies exist regarding gender assignment, sex of rearing, and surgery [10]. One critical issue is the fate of the testicles: Should they be kept in place until the hypothetical age of self-gender determination? Or if female sex rearing is decided on, should they be removed early to avoid pubertal virilization? If conservative management is chosen, temporarily blocking pubertal virilization with a GnRH analog until gender-identity development is settled is an option.

The risk of gonadal tumor is small and probably equals the risk recorded with undescended testes.

Gonadal dysplasia or dysgenesis is characterized by failed production of androgens and AMH responsible for a poorly developed genital tubercle (usually severe