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Hermaphroditism in the Common Orthopaedic Practice: A Review

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Abstract

Disorders of sex development result in problems concerning the sex assignment of the child. The evaluation and management of patients with ambiguous genitalia requires a multidisciplinary team including neonatologist, pediatrician, urologist, endocrinologist, pediatric surgeon, geneticist, gynecologist and psychiatrist or psychologist depending on the age of the treated patient. Although the orthopaedic surgeon is not involved in the primary treatment of these patients, he may be helpful towards making an early referral indicating a child's undiagnosed clinical sign or may occasionally be involved in the treatment of coexisting traumatic lesions or disorders in adult patients.

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In humans, male or female phenotype develops through a cascade of processes which initiate with sex determination and follow with sex differentiation. The karyotype (46, XY or 46, XX) of the embryo (genetic sex) determines whether bipotential primordial gonads differentiate into a testis or an ovary, respectively (gonadal differentiation). This is a complex developmental process involving various genes and hormones. The sex-determining region of the Y chromosome (SRY gene) produces a protein that activates a gene network, which directs the gonads to develop as testes; when it is absent the gonads develop as ovaries. Similarly, internal and external genital organs develop from an indeterminate (undifferentiated) stage from the complex differentiation of the two primitive ducts: the Wolffian and Müllerian ducts. Once the gonad begins to develop as a testis, the two support cells in the testis differentiate: the Leydig cells produce testosterone and the Sertoli cells produce Müllerian inhibiting substance also known as anti-Müllerian hormone.

Differentiation of the Wolffian ducts, urogenital sinus, and external genitalia is androgen dependent. Female sex differentiation appears to be a more passive process that is independent of estrogen. However, several genes have been shown to be necessary to initiate ovarian development, and to actively repress the gene network that promotes testis development. Hormonal production of differentiated gonads is relevant for differentiation of the internal and external genitalia during fetal life, and for the development of secondary sex characteristics at puberty [1,2].

There are four main types of genital anomalies: true hermaphroditism, male or female pseudohermaphroditism and gonadal dysgenesis [3,4].

In biology, a hermaphrodite is an organism that has reproductive organs of both male and female sexes. The term derives from ancient Greek: hermaphroditos (ἑρμαφρόδιτος), the son of Hermes and Aphrodite in Greek mythology. True hermaphroditism, also known as ovotesticular disorder of sex development, is reserved for the very rare cases where both ovarian and testicular tissues are present [5]. The term pseudohermaphroditism was created by Klebs in 1876. It is the condition in which an organism is born with primary sex characteristics of one sex but develops the secondary sex characteristics that are different from what would be expected on the basis of the gonadal tissue (ovary or testis). The diagnosis of pseudohermaphroditism can be made in utero by comparing the karyotype obtained by amniocentesis with the external genitalia of the fetus during a prenatal ultrasound [6].

Male pseudohermaphroditism is a condition in which individuals with a XY karyotype and testes appear with a complete or partial female phenotype, and female pseudohermaphroditism is the presence of complete or partial male phenotypes in individuals with a XX karyotype and ovaries. The term "intersexuality" was introduced by Goldschmidt in 1923 to replace pseudohermaphroditism, but it has also been challenged and replaced by a nomenclature system based on disorders of sex development (DSD), which covers "congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical" [7]. The diagnostic investigation of a patient with a genital malformation or phenotype that does not match the chromosomal sex requires additional phenotypic information using metabolic and endocrine testing, imaging studies and genetic analysis.

Genetic technologies have resulted in the discovery of many genes involved in sex determination. Genes involved in sex determination have been isolated by positional cloning using patient samples in which microscopically visible chromosomal alterations were identified using standard cytogenetic techniques [8-10]. The use of linkage analysis is restricted due to the small number of patients and the lack of large number of individuals involved in families. New genomic technologies may be used as a first-stage diagnostic technique because they allow for early identification of a genetic cause that may be critical for patient management. Recent advances of chromosomal microarray and exome sequencing technologies are allowing for higher rates of diagnostic success [11-13].

Male pseudohermaphroditism is due to hypoandrogenism in XY individuals [14,15]. Deficit in the presence and in the action of androgens is due to different conditions that can be divided into three main categories:

1) androgen resistance: it is the main cause of male pseudohermaphroditism and it leads to the androgen insensitivity (testicular feminization) syndrome, 2) deficit in the production of testosterone and 3) deficit in the production of dihydrotestosterone [16].

The androgen insensitivity syndrome was defined by Morris in 1953 [17,18]. It is a rare inherited disorder that leads to partial or complete lack of response to androgens caused by a receptor dysfunction. The condition of androgen insensitivity is due in the great majority of cases to point mutations or micro deletions in the androgen receptor gene [19-22].

Androgen insensitivity syndrome can be divided into three categories based on the genital phenotype:

1) Complete androgen insensitivity syndrome (CAIS) is a condition of complete inability of the cell to respond to androgens. The resistance of cell toward testosterone and its more potent androgen metabolite dihydrotestosterone prevents the complete masculinization of male genitalia in the developing fetus and the development of male secondary sexual characteristics with absence of pubic or axillary hair at puberty. Individuals with complete androgen insensitivity, as well as individuals with severe deficit in testosterone production are born with a complete female phenotype, despite having a 46, XY karyotype [23,24].

The typical presentation is either primary amenorrhoea in adolescence, or inguinal swellings in an infant. Therefore, prepubertal girls with inguinal hernia should be carefully examined to exclude the syndrome [25]. Ultrasonography and magnetic resonance imaging are used to locate non-palpable testis [26].

2) Partial or incomplete androgen insensitivity syndrome (PAIS) was described in 1963 [27]. It consists in the partial inability of the cell to respond to androgens. There is a wide spectrum of clinical phenotypes in which the external genitalia are predominantly male,

ambiguous or predominantly female. Patients who present predominantly male phenotypes may present small penis, cryptorchidism, bifid scrotum and hypospadias.

Patients with predominantly female phenotypes may present normal female genital phenotype with pubic and/or axillary hair at puberty or essentially female phenotype with separate urethral and vaginal orifices, mild clitoromegaly or labial fusion. Patients with ambiguous phenotype (Figure 1) may present with a phallic structure intermediate between penis and clitoris, urogenital sinus with perineal orifice and labioscrotal folds and severely limited masculinization [28-30].

3) Mild androgen insensitivity syndrome (MAIS) is a condition of mild inability of cells to respond to androgens. Individuals with mild androgen insensitivity syndrome are born phenotypically male, according to their XY karyotype. They have fully masculinized genitalia and their problems are mostly related to the condition of infertility (oligospermia or azoospermia), decreased secondary terminal hair, and high pitch of voice. The external male genitalia (penis, scrotum, and urethra) are normal, as well as internal genitalia, including Wolffian structures and prostate. However testicular volume can be diminished due to the condition of infertility [31-34].

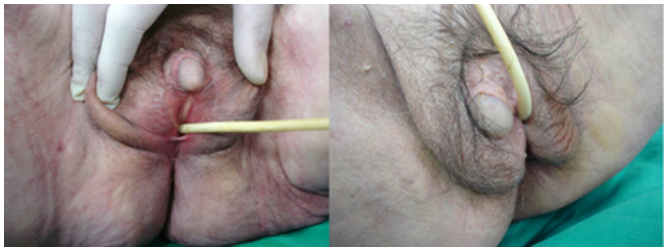

Figure 1: *An 80-year-old patient, with ambiguous genitalia since birth, was treated for a hip fracture. Bilateral orchiectomy was reported at 13 years of age. The chromosome studies showed a 46, XY normal male pattern. The patient was diagnosed with partial androgen insensitivity syndrome (formerly known as testicular feminization syndrome). Diagnosis was based on the small penis (closed external urethral orifice), testes, a double blind ended vagina and poorly developed labia, in association with normal male chromosomes.*

Female pseudohermaphroditism may be due to: 1) Hyperandrogenism that is caused by excess of androgens of extragonadal origin (Figure 2). The main cause of accumulation of androgens is congenital virilizing adrenal hyperplasia, and 2) Deficit in the synthesis of estrogens that eventually results in a similar accumulation of androgens.

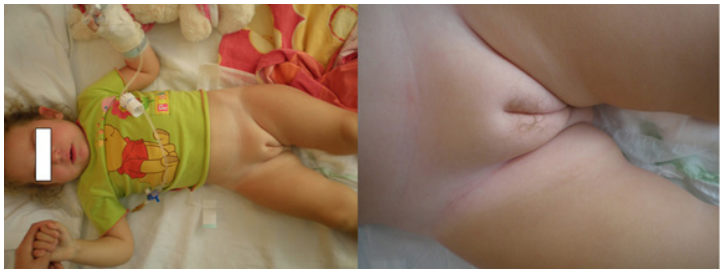

Figure 2: *A 22-month-old girl that presented with a painful hip. The diagnosis of premature adrenarche was based on the clinical appearance of pubic hair (pubarche), 3 months ago, and biochemically on the elevated adrenal androgen concentrations.*

The presence of testosterone and other androgens during fetal live of female fetuses with a XX karyotype, obviously leads to genital ambiguity due to partial masculinization of external genitalia. The high levels of testosterone result in clitoromegaly [28]. In addition, the vaginal opening can be closed, as well as female urethra, while a male urethra can appear inside the phallus. The most severely affected female infants can even appear as a real male [35,36].

Gonadal dysgenesis includes the Turner syndrome, the pure gonadal dysgenesis (Swyer syndrome), the asymmetrical gonadal differentiation, and the gonadal dysgenesis of some forms of trisomy. It may be associated with sensorineural deafness in females, and deafness in affected males (Perrault syndrome) [37-39].

The diagnostic process in cases with ambiguous genitalia requires evaluation by a skilled multidisciplinary team including clinical, imaging, hormonal, genetic and molecular examination with an apparent shift, recently, towards molecular genetic testing to reach a correct diagnosis [40,41]. Several cases without etiologic diagnosis or with syndromic features need advanced investigation [42-45]. Physical examination is the key to diagnosis and the search for gonads with palpation and imaging is the first element [46].

The diagnosis of female pseudohermaphroditism seems advisable when gonads are absent. A diagnosis of male pseudohermaphroditism is more appropriate whenever they are palpated. Karyotyping may indicate the presence of a Y chromosome, while the gene for the determination of maleness in the sex determining region on the short arm of the Y chromosome may be identified. Hormonal investigation of 17-OH- progesterone will confirm the diagnosis of congenital adrenal hyperplasia due to deficiency in 21-hydroxylase. Testicular stimulation with human chorionic gonadotropin will determine the functional value of testicular tissue. Whenever testosterone rises normally androgen resistance is indicated, but if it does not rise after the test testicular dysgenesis or disturbance in testosterone biosynthesis may be responsible.

In cases of female pseudohermaphroditism, the newborn should always be declared to be of female sex, while in cases of male pseudohermaphroditism, great care should be taken in the declaration of male sex [47]. Prompt evaluation of the newborn with ambiguous genitalia will permit the detection of life-threatening conditions (salt-losing crisis due to congenital adrenal hyperplasia or Wilm's tumour) [48]. Hormonal therapy forms part of the treatment of every intersex condition [49]. Judicious hormonal supplementation based upon type of the disorder and gender assigned can provide a psychological and cosmetic benefit to patients [50].

Surgical treatment is a source of major concern regarding timing, choice of the individual and irreversibility of surgical procedures [51,52]. The diagnosis of disorders of sex differentiation raises concerns of tumor risk and treatment as well as future fertility preservation. The management of such patients is complex and evaluation of tumor risk is aided by advances in genotyping for Y-chromosomal material not evident in traditional karyotyping. The necessity of prophylactic gonadectomy in all patients with Y chromosome is stressed because of a close association with the arising of tumors in the dysgenetic gonads. Future studies utilizing more advanced histologic examination of gonads will improve our understanding of the true incidences of malignancy in this diverse population [53-55].

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