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How should we classify intersex disorders?

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Abstract The term disorders of sex development (DSD) has achieved widespread acceptance as replacement for the term intersex, but how to classify these conditions remains problematic. The LWPES-ESPE (Lawson Wilkins Pediatric Endocrine Society and European Society of Paediatric Endocrinology) Consensus Group proposed using the karyotype as a basis for classification; however, this is but a crude reflection of the genetic makeup, is diagnostically non-specific, and is not in itself relevant to subsequent clinical developments. The historical classification of intersex disorders based on gonadal histology is currently out of favor, being tainted by association with the terms hermaphroditism and pseudohermaphroditism. We believe this is regrettable, for the histology of the gonad remains fundamental to the understanding of normal and aberrant sexual development by medical students and residents in training, as well as being a major determinant of clinical outcome for the patient.

We propose a comprehensive classification of those DSD conditions generally regarded as belonging under the heading of intersex, based on gonadal histology. Biopsy will not be required when the diagnosis is clearly established biochemically or by gene studies as the histology can be confidently predicted. It will only be required when an ovotestis or dysgenetic gonad is suspected in order to determine the definitive diagnosis.

The term intersex has been used by generations of physicians to describe a specific subset of the disorders of sexual differentiation, which frequently result in an ambiguous appearance of the external genitalia. Most are distinguished from other genital malformations by a clearly defined aberration in the endocrine cascade responsible for normal development of the fetal internal and external genitalia, and so have the potential to cause life-threatening metabolic disturbances, inappropriate physical changes at puberty or confusion with gender identity. In some cases, the gonads also have the propensity to undergo malignant change.

Unease, however, has long been felt regarding the term intersex, with its connotation that such patients are somehow in an 'in between' state, whereas the terms female pseudohermaphrodite, true hermaphrodite and male pseudohermaphrodite place these patients outside the mainstream of society, relegating them to the realm of mythology. Understandably, therefore, there have been

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repeated calls for the abandonment of these demeaning terms. Recently, Dreger and colleagues proposed replacing intersex with the non-pejorative term disorders of sexual differentiation [1].

The challenge of devising a satisfactory terminology and classification for intersex conditions was recently taken up by a consensus group convened jointly by the Lawson Wilkins Pediatric Endocrine Society and The European Society of Paediatric Endocrinology (LWPES-ESPE) to address various aspects of this group of disorders [2,3]. Although they endorsed Dreger's sentiment regarding terminology, they preferred the term disorders of sex development (DSD) which has rapidly achieved widespread acceptance; however, they did not specify precisely which conditions should be considered under this heading. Hughes [4] subsequently published a list of disorders in which sex development is aberrant, but included, in order to be comprehensive, various conditions (e.g. simple hypospadias, undescended testis and micropenis on the one hand, and cloacal anomaly variants, vaginal agenesis and labial adhesions on the other) none of which carry the potential long-term complications of the conditions traditionally grouped under the heading of intersex [5]. We believe this important distinction can be maintained if the term 'DSD' be regarded as standing for 'discordant sex development', rather than disorders of sex development.

Although it is conceptually attractive from the scientific perspective to base the classification of intersex disorders on the specific underlying genetic error, our current knowledge in this regard is insufficiently complete to allow this to be done in a comprehensive fashion. Recognizing these limitations, the Consensus Group favored using the karyotype as the overarching basis for classification. However, their proposed nomenclature, which broadly divides intersex conditions into 46XX DSD and 46XY DSD, could not readily accommodate true hermaphroditism, in which the karyotype may be 46XX, 46XY, 46XX/46XY or other variants, nor patients with dysgenetic gonads in which a 45X line is frequently present (Fig. 1).

Although it is readily obtainable, the karyotype is of limited diagnostic value because of the considerable overlap in the patterns found among various underlying intersex conditions. For example, a patient with a 46XX karyotype may have any of the conditions historically listed under the heading female pseudohermaphroditism, but might also have true hermaphroditism. Conversely, a patient with a 46XY karyotype may have any of the conditions traditionally listed under the heading male pseudohermaphroditism, but might alternatively be harboring ovotestes or gonads which are dysgenetic.

TRADITIONAL	LWPES/ESPE	PROPOSED
FEMALE PSEUDOHERMAPHRODITE	46XX DSD	OVARIAN DSD
TRUE HERMAPHRODITE	OVOTESTICULAR DSD	OVOTESTICULAR DSD
MALE PSEUDOHERMAPHRODITE	46XY DSD	TESTICULAR DSD
DYSGENETIC MALE PSEUDOHERMAPHRODITE	46XY DSD	DYSGENETIC DSD

Figure 1 Three schemes for classifying intersex conditions compared.

In contrast to the karyotype, the histological integrity of the gonads and their consequent function have been universally recognized, ever since the classical experiments of Jost [6] over 60 years ago, as fundamental to normal sexual differentiation and the subsequent physiological and anatomical changes which will occur in postnatal life. Thus, those with histologically normal ovaries have at least the potential to be sexually active and fertile women, once any underlying hormonal imbalance has been corrected and suitable surgery carried out. Those with histologically normal testes can be expected, in the absence of severe androgen insensitivity, to show some virilization at puberty with enlargement of the penis, whereas those harboring both testicular and ovarian tissue are likely to develop a conflicted phenotype at puberty as a result of a surge in both testosterone and estrogen production. Of particular long-term importance is the risk of the gonads undergoing malignant degeneration, this potential being particularly high when attempted differentiation has resulted in dysgenetic gonadal tissue.

A proposed classification

We recommend that the term DSD be strictly limited to those conditions traditionally regarded as intersex, and that these should be classified on the basis of their underlying gonadal histology. Four distinct groups are proposed as follows. In Fig. 2(a—d), the definitive underlying diagnoses within each category are illustrated.

Ovarian DSD, in which the gonads are composed of normal ovarian stroma embedded in which are numerous follicles, thus having the potential for normal hormonal function and ovulation.

Ovotesticular DSD, in which the gonads comprise both ovarian and testicular tissue distributed either separately in two distinct gonads, or within a single gonad with either a bipolar arrangement or as a diffuse admixture of ovarian and testicular elements. The ovarian element must contain at least one well-defined follicle. The testicular component comprises architecturally ordered tubules, although the intervening stroma may be more abundant than normal.

Testicular DSD, in which the semeniferous tubules are normal in configuration and cell type, although Leydig cells may be prominent.

Dysgenetic DSD, in which the tubules are disordered and often sparse, in distinct contrast to testicular DSD, with an abundance of stromal tissue; because of the strong propensity for such gonads to undergo malignant degeneration, we believe this group requires classification as a distinct entity.

Discussion

Ideally, the classification of medical conditions should bring together those with shared fundamental characteristics, where possible based on their etiology. Among the wide range of aberrations affecting the appearance of the genitalia, those that are caused by a well-defined error in the pathway of sexual differentiation during the first trimester clearly belong together. Furthermore, their