How should we classify intersex disorders?

Ieuan Hughes

Department of Paediatrics, University of Cambridge, Cambridge CB2 2QQ, UK

Received 24 March 2010; accepted 7 April 2010
Available online 1 June 2010

It is a tall order to expect 50 experts on a subject in medicine to reach unanimity when tasked with devising an alternative nomenclature and classification system for a set of conditions that manifest as intersex at birth or at puberty with somatic sex characteristics discordant with sex assignment. Yet, that was attempted in 2005 and realized as what has now become known as the Chicago Consensus on management of intersex disorders [1]. The task was approached using the strategy of consensus decision making, which involves reaching general agreement or an accord amongst a group of individuals. While it is acknowledged that some participants may express divergent views, they are nevertheless willing to accede to the ethos that the sum of the parts is more important than the individual components. This enables a concordat to be reached for which the group as a whole is responsible. When such a consensus document reaches the public domain, it is inevitable that experts in the subject area will exercise their right to dissent over certain elements. Such debate is to be welcomed, for which an opportunity has arisen in this issue of the Journal based on the paper by the Aaronsons [2].

The authors acknowledge that the acronym DSD for disorders of sex development, a generic term that was never intended to have the same connotation as the term intersex, has been rapidly and widely accepted. That is indeed the case, based on a recent survey of 60 centres in Europe who care for families with DSD and evidence of widespread usage of the acronym in the medical and scientific literature [3,4]. However, their dissent focuses on the proposed classification system, which merely uses DSD as a handle on which to hang just three simple starting subgroups defined by the sex chromosomes. The list of conditions included in each subgroup can be as lengthy as one wishes, particularly in the XY DSD category. Many are not what previously would be considered as intersex, but DSD are not defined in that vein. This is a distinction that the authors have failed to grasp when arguing that conditions such as simple hypospadias, cryptorchidism, cloacal anomalies and labial adhesions are not examples of intersex. Of course they are not, but they are disorders of sex development; even the common labial adhesion which can completely occlude the vaginal opening is not a ‘trivial’ matter for the mother who is concerned that her daughter does not have a normal vagina.

So what is the basis for the authors now proposing an alternative classification system for DSD and what are its merits? It is argued that the starting point should not be sex chromosomes as this is unreliable as a diagnosis. But knowing that a karyotype is XX in an infant with DSD is not a diagnosis, it merely steers the investigator towards one of the three subgroups. The first subgroup defined as a sex chromosome anomaly will be readily identified by examples such as 47XXY, 45XO/46XY, 46XX/46XY and several other cases of aneuploidy that can arise. Where this karyotype-based approach fails, the authors argue, is in conditions such as ovotesticular DSD (true hermaphroditism) where the karyotype can be 46,XX (most commonly), 46,XY or 46XX/46XY, and the external phenotype quite variable. This is an argument for classifying causes of DSD according to the gonad type. But, how practical is that as a diagnostic starting point when the clinician is faced with a newborn with genitalia sufficiently ambiguous to render sex assignment impossible at birth? Yes, histological examination of the gonads is the only certain diagnostic test for ovotesticular DSD, but that has always been the case whichever classification system has been used. One would hope that
the dysgenetic DSD could be defined with equal clarity but unless there is obvious evidence of a ‘streak’ gonad on histology, too often the clinician is provided with a report that documents changes in a testis akin to that found in an undescended testis. That is hardly a diagnosis that sheds light on the mechanism of a defect that could have arisen along a pathway of sex determination through to sex differentiation. So, would the proposed classification illustrated in the figures and based on gonadal histology stack up as a practical guide to deciding where to start with investigating a newborn with ambiguous genitalia?

The reality is that all newborns with atypical external genitalia will have a karyotype performed. This is now almost as readily available as a blood glucose test. Indeed, the use of fluorescent in-situ hybridization (FISH) has revolutionized the initial investigations, providing an indication of the sex chromosomes within hours of birth. Increasingly, conditions such as complete androgen insensitivity syndrome and some androgen biosynthetic disorders are being detected through a mismatch between prenatal genotype and the phenotype at birth. Knowledge of the karyotype is key to resolving such dilemmas. The authors have referred to conditions such as congenital adrenal hyperplasia (CAH), where knowledge of the gonad type need only be implied indirectly. But that is a case in point, where correct use of only a few tests is diagnostic: a FISH showing the presence of two X-centromeric probes and an absence of the Y-related SRY probes lighting up; a cervix/uterus evident on ultrasound and a markedly elevated serum 17O-progesterone level. That is game, set and match for CAH due to 21-hydroxylase deficiency, the commonest cause of ambiguous genitalia of the newborn. If the 17O-progesterone is normal, then a possible diagnosis would be ovotesticular DSD for which the definitive diagnostic test in due course would be laparoscopy and gonadal biopsies.

The power of modern molecular techniques is illustrated by a recent case of severe hypospadias, micropenis, bifid scrotum with no palpable testes investigated by this author. The FISH probes suggested four X chromosomes in the presence of a Y chromosome, subsequently confirmed within days by the karyotype 49,XXXXY. This indicates a rare sex chromosome aneuploidy disorder that is effectively a variant of Klinefelter’s syndrome and firmly fits within one of the three categories of the DSD classification.

This author does not wish to give the impression that gonadal histology is not important in the context of DSD and their investigation. It is essential to demonstrate the presence of both ovarian (follicles demonstrated) and testicular tissue in some examples of DSD, and to predict the risk of gonadal tumours. In this context, there have been major advances in the use of immunohistochemistry, using a battery of new markers to identify pre-malignant conditions such as carcinoma in situ. Histopathologists working in DSD centres should be encouraged to incorporate these advances into their clinical practice so that what is now loosely labelled as a ‘dysgenetic’ testis is given added substance. The Aaronsons argue that the most compelling argument to usurp the current DSD classification model and place gonadal histology as the starting point is greater clarity when teaching this subject to students and postgraduate trainees. The Part II Medical Sciences Tripos in Cambridge provides a popular course entitled ‘Mechanisms of Disease’ in which lectures on DSD have figured in recent years using the current classification. Student feedback is universally satisfactory, and the course complements the lectures already provided in reproductive science, systems biology and pathology. For the postgraduate trainee and specialists involved in research, the DSD nomenclature and the classification system which it spawned have been cemented in major programmes of research underway in Europe (the EuroDSD programme), in standard textbooks of endocrinology, and in recent monographs on DSD [5,6]. With such a head of steam having emerged as a consequence of the Chicago Consensus and the remarkably rapid and widespread adoption of its principles into clinical practice, the proposals proffered in this paper are not sufficiently robust to make the case for changing what has now become the status quo. This is not to denigrate the seminal observations of Klebs in the 19th century which led him to coin the term pseudohermaphroditism. Surely the Aaronsons are not proposing we take a retrograde step by resurrecting this term which is confusing to health professionals and patients alike. Klebs did not have the luxury of genetic and biochemical knowledge as applied to DSD. We do, so let us not waste the opportunity that a modern medical lexicon allows to make further strides to establish aetiology in so many examples of DSD.

References


