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REVIEW ARTICLE

The role of the pediatrician in the management of children with genital ambiguities

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Abstract

Objective: To present the diagnostic criteria of genital ambiguity, the initial medical management and the attitude expected of pediatricians.

Sources: Review of the scientific literature in the form of articles indexed on MEDLINE, in English and Portuguese, published between 1990 and 2007 and dealing with the pediatric age group.

Summary of the findings: Pediatricians have a fundamental role to play in the assessment of genital ambiguity, the purpose of which is to arrive at an etiologic diagnosis in the shortest possible time in order to define the patient's sex and plan treatment. There are specific diagnostic criteria, but, in general, genitalia are ambiguous whenever there is difficulty in attributing gender to a child. The pediatrician should inform the patient's family that assignment of their child's sex will depend upon detailed laboratory investigations, preferably carried out by a multidisciplinary team at a tertiary service. The 46,XX or 46,XY karyotypes are not alone sufficient to define the gender of rearing, although the test is fundamental to guide the investigation. When there are no palpable gonads, the first hypothesis should be congenital adrenal hyperplasia. Other causes included partial androgen insensitivity, 5α-reductase deficiency, partial gonadal dysgenesis and hermaphroditism. The family should be provided with support and information throughout the assessment process, and their participation is fundamental in the decision of which gender to rear the child in.

Conclusions: Although cases of genital ambiguity are relatively rare for pediatricians, they should be well-informed on the subject and the correct management of these conditions, since they will often be responsible for the initial guidance that families receive and for maintaining contact between them and the multidisciplinary team.

J Pediatr (Rio J). 2007;83(5 Suppl):S184-191: Ambiguity, determination, differentiation, genitalia, intersex.

Introduction

Pediatricians faced with a child with genital ambiguity (GA) must be conscious of the importance of their role in a situation that is still surrounded by prejudice and which has serious medical, psychological and social implications. Furthermore, management of disorders of sex development (DSD) demands great sensitivity, in order that, over the long term, there is no confusion over the child's gender identity.[1,2]

The major challenge with DSD patients is to reach a precise etiologic diagnosis in the shortest time possible. On this diagnosis will depend not only the definition of sex, but also all of the subsequent treatment procedures and even the genetic counseling the patient's family will receive.[1,2]

In all cases it is of fundamental importance that diagnosis be made before gender identity is established. The ideal scenario is for this investigation to be undertaken during the neonatal period, with potentially lethal cases detected at this point, such as the salt-wasting form of congenital adrenal hyperplasia, minimizing psychological and social problems.[1-4]

This investigation will require the involvement of many different healthcare professionals – pediatrician, endocrinologist, geneticist, surgeon, gynecologist, radiologist, pathologist, forensic physician, psychologist (or psychiatrist)

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and social worker. By working together in an integrated manner, these professionals are not only able to decrease the time taken for diagnosis, but also to standardize the information passed to the family and, consequently, increase confidence in the medical team as a whole. Furthermore, concentrating these cases at tertiary services, such as university hospitals, makes it possible for patients and their families come into contact with others with similar experiences.[1,2,5,6]

When a newborn is identified as having GA, the behavior of the "first doctor" – a pediatrician or neonatologist – when dealing with the family is of fundamental importance since their word may be taken as the "absolute truth" and the effect can be difficult to undo if the information given is incorrect. By calmly explaining that there is no immediate way of defining the child's sex and that this definition will depend on detailed laboratory investigation, some of the "scars" that could otherwise occur can be avoided.[1,2]

As those who treat children with DSD know, one of the most critical moments for parents in this entire process is, undoubtedly, the point at which they are informed their child's sex is indeterminate. Barbara Thomas is coordinator at the German association XY-Frauen which supports women whose genetic gender is male and, during a lecture she delivered in Lübeck, Germany, in 2006, she suggested that: "Before anything else, tell the parents that they have a beautiful and healthy baby".

When GA is identified soon after birth, the family should be immediately informed of the genital abnormality, of the need for evaluation by experienced professionals who will perform specialized tests (generally to be found at university hospitals) and therefore of the need to delay registering the birth.[1,2,5,6]

Understanding normal sex determination and differentiation

In order to be able to explain to the family the cause of GA, the pediatrician (or other healthcare professional) must themselves understand the genetic and hormonal factors responsible for normal development of gonads, internal genital ducts and external genitalia.[1,2]

Up until around 7 weeks after fertilization, the human embryo is a bisexual organism, equipped with primordial gonads and genitals that are identical in both sexes, meaning it is impossible to distinguish either macroscopically or microscopically between embryos that are predestined to be male or female. This state of neutral gender is manifest as rudimentary gonads (undifferentiated gonads), primordial internal male and female genital ducts (Wolffian and Müllerian ducts, respectively) and rudimentary external genitals (genital tubercule, urogenital ridges, labioscrotal folds and urogenital sinus).[7-9]

Depending upon the genetic gender of the embryo (46,XY or 46,XX), either testicles or ovaries will form, a process known as sexual determination; sexual differentiation refers to process subsequent to gonad formation, i.e. the emergence of internal and external genitals.[7-9]

The role of the Y chromosome as the determinant of masculinity has been known since the end of the 1950s, when study of the human karyotype began. Then, analysis of people with a variety of numerical and structural aberrations of sex chromosomes indicated the existence of a region on the short arm of the Y chromosome specifically involved in testicular differentiation. Finally, molecular studies of 46,XX men whose paternal X chromosome contains a segment of the short arm of the Y chromosome and of 46,XY women with microdeletions in this region made it possible to arrive at the *SRY*-gene (sex-determining region on the Y chromosome), which is located at the 1A1 region of the short arm of this chromosome and plays a fundamental role in determination of the testicle from the undifferentiated gonad. Later studies, however, demonstrated that male gonadogenesis is a very complex process, depending on other genes present in autosomes and the X chromosome too.[10-12]

In embryos whose genetic gender is male (46,XY), at around the seventh week, the presence of the *SRY*gene makes the Sertoli cells differentiate from epithelial cells and aggregate, forming cords around the primitive germ cells– which thereby become spermatogonia. These cords develop and form seminiferous tubules, tubuli recti and the rete testis. Leydig cells can be observed in the interstitial space between the tubes from week eight onwards.[7-9]

Once the testicles have differentiated, they are responsible both for controlling degeneration of primordial female internal genitals and for differentiation of male internal conduits and external genitals. From the seventh week on, the Sertoli cells secrete Anti-Müllerian hormone (AMH), which induces degeneration of the Müllerian ducts, the remnants of which are the prostatic utricle and appendix testis. The action of AMH is paracrine-mediated and each testicle is responsible for destroying the Müllerian duct on its side.[13] From the eighth/ninth week on, Leydig cells begin to produce testosterone, which stabilizes the Wolffian ducts and allows them to differentiate into the epididymis, vas deferens, seminal vesicle and ejaculatory duct. The local action of testosterone on the Wolffian ducts is much more important than its systemic action, to the extent that each testicle is also responsible for the differentiation of the Wolffian duct on its own side [14] The prostate emerges, around the 10th week, by evagination from the urogenital sinus.[8]

Testosterone is converted by the type 2 5α-reductase enzyme into dihydrotestosterone (DHT), the most potent of the androgens which virilizes the rudimentary external genitalia between the ninth and 12th weeks of gestation. In response to this hormone, the genital tubercule gives rise to the glans penis and the corpus cavernosi; the urogenital ridges

lengthen together with the tubercule and fuse to form the corpus spongiosum; the labioscrotal folds fuse along the medial line, giving rise to the scrotum; and the urogenital sinus results in the penile urethra. At the glans, ectodermic invagination forms the balanic portion of the urethra, which will only join up with the penile part at around the 12th week; the foreskin almost completely surrounds the glans by around the 14th week. The testicles migrate from the pelvic cavity down to the scrotum, starting at around the 28th week and completing by around the 32nd.[7-9]

Human chorionic gonadotropin (hCG) is produced by syncytiotrophoblasts, stimulating Leydig cells to secrete testosterone during the critical period of male sex differentiation. From this point onwards, the fetus's own luteinizing hormone (LH) is necessary for continued stimulation of the Leydig cells, in order to promote complete testicular descent and penile growth.[7-9]

In embryos whose genetic gender is female (46,XX), the absence of *SRY* means that the gonads remain undifferentiated up until the end of the 10th week, when the ovaries begin to differentiate. For ovarian maintenance, two entire X chromosomes are needed, and if this is not the case, the process of ovarian follicle degeneration is accelerated and the gonads become dysgenetic, i.e. they are made up only of conjunctive tissue, without the elements from the germinative lineage.[7-9]

Since AMH is not produced, the Müllerian ducts develop and form the female genital tract (uterus, Fallopian tubes and upper portion of the vagina). In the absence of high local androgen concentrations, the Wolffian ducts do not differentiate and remain as embryonic vestiges (epoophoron, paroophoron, Gartner's ducts). In the absence of stimulation from DHT, the genital tubercule gives rise to the clitoral glans and body, the urogenital ridges to the labia minora, the labioscrotal folds to the labia majora, and the urogenital sinus divides to form the female urethra and the lower part of the vagina.[7-9]

Definition of genital ambiguity. Who should be investigated?

A newborn infant with GA constitutes an emergency situation in which pediatricians must concern themselves both about possible short-term complications – since some etiologies, such as the salt-wasting form of congenital adrenal hyperplasia and certain malformation syndromes can potentially be lethal – and also about the long term, since failures in the process of defining sex can cause irreparable damage to patients and their families.[1,2,5,6,15]

However, physicians do not always pay due attention to examining the genitalia of newborns and, in many cases, genital anomalies are found by a family member. Knowledge of normal variation is important, since less experienced professionals could confuse variation with GA, as in cases where the clitoral hood is more developed but there is no cavernous tissue which does not denote clitoral hypertrophy, or where excess pubic adiposity may give a false impression of micropenis. In contrast, if gonads are not palpable in genitalia of male appearance, which will frequently be considered to be simply bilateral cryptorchidism, the patient may actually be a girl presenting with congenital adrenal hyperplasia with an extreme degree of intrauterine virilization.[1,2,5,6]

Twin findings of cryptorchidism and hypospadia should be taken as an even stronger warning by the pediatrician. In 1999, Kaefer et al.[16] assessed 79 patients among whom the incidence of DSD reached 32%. When gonads were not palpable during clinical examination, the risk of DSD was three times greater than when gonads were palpable. In an analogous manner, the more severe the degree of hypospadia, the greater the probability of detecting a DSD. Therefore, in cases such as these, the safest course is to refer the child to a specialized service for diagnostic assessment.

The diagnostic criteria proposed by Danish[17] in 1982 is one of the most often cited in the literature and is easily applicable in medical practice. According to this classification, there is GA if any of the following characteristics are observed.

In genitalia apparently male in appearance: (1) gonads not palpable; (2) stretched penis size below - 2.5 standard deviations from the mean for age (Table 1); (3) small gonads, i.e. largest diameter smaller than 8 mm; (4) presence of an inguinal mass (which could correspond to rudimentary uterus and Fallopian tubes); (5) hypospadia.

In genitalia apparently female in appearance: (1) clitoral diameter greater than 6 mm; (2) palpable gonad within labioscrotal fold; (3) posterior labial fusion; (4) an inguinal mass which could correspond to testicles.

According to Danish, any one of the findings mentioned is sufficient to arouse suspicion of GA, meaning that cases of hypospadia or bilateral cryptorchidism in isolation should be investigated to avoid failing to diagnose a DSD.

Without fixing on rigid criteria, it can be stated that genitalia are ambiguous whenever they present difficulty for a physician (assumed to be knowledgeable of the normal variation of external genitalia) to be able to define a child's sex. It is, however, fundamental to differentiate GA from genital malformation, such as epispadia, partial or total penis-scrotum inversion and agenesis of the penis or clitoris, which should not be considered as DSD.[1,2,5,6]

The importance of clinical history and physical examination

During anamnesis, the gestational history should be assessed, with special attention to use of medication and any signs of maternal virilization; history of low birth weight;[18] family history, such as parental consanguinity, similar cases, early or delayed puberty, infertility and arterial hypertension

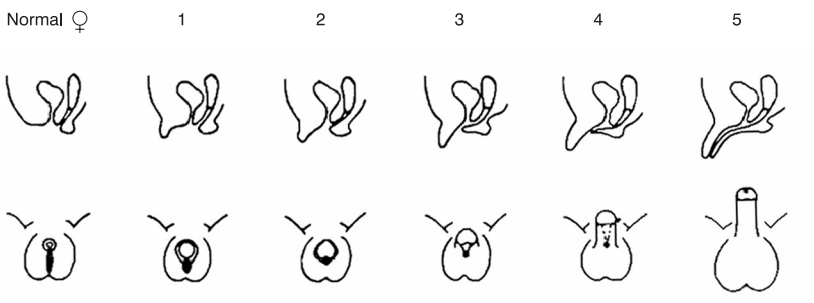
Table 1 - Penis sizes (in cm) by age

Age	Mean ± SD	Mean - 2.5 SD
NB at 30 weeks	2.5±0.4	1.5
NB at 34 weeks	3.0±0.4	2.0
NB to term	3.5±0.4	2.5
0-5 months	3.9±0.8	1.9
6-12 months	4.3±0.8	2.3
1-2 years	4.7±0.8	2.6
2-3 years	5.1±0.9	2.9
3-4 years	5.5±0.9	3.3
4-5 years	5.7±0.9	3.5
5-6 years	6.0±0.9	3.8
6-7 years	6.1±0.9	3.9
7-8 years	6.2±1.0	3.7
8-9 years	6.3±1.0	3.8
9-10 years	6.3±1.0	3.8
10-11 years	6.4±1.1	3.7
Adult	13.3±1.6	9.3

NB = newborn; SD = standard deviation.

during childhood or unexplained deaths during the first months of life, among others.[1,2,5,6,19,20]

On the subject of physical examination, it should be borne in mind that "the findings of genital examination do not define etiologic diagnosis but may prioritize testing." A search should be performed for dysmorphisms or malformations (particularly of the spine and anorectal area) that constitute syndromes and external genitalia should be assessed. With the older children, it is also important to assess nutritional status, arterial blood pressure, the presence of pubic hair, acne and signs of puberty. External genitalia should be assessed and the degree of virilization classified (Figure 1), analyzing the size of the phallus; position of urethral meatus; the presence of vaginal introitus or urogenital sinus opening; degree of fusion, symmetry, pigmentation and wrinkling of the labioscrotal folds; and the presence of inguinal masses and the location and size of gonads.[1,2,5,6,15,19,20]



Grade 1 = genitalia of female appearance, with just an enlarged phallus; Grade 2 = phallus further enlarged, associated with posterior fusion of the labioscrotal folds, without a urogenital sinus; Grade 3 = significant increase in phallus size, associated with almost complete fusion of the labioscrotal folds, and the presence of a urogenital sinus with perineal opening; Grade 4 = phallus with penile appearance, associated with complete fusion of labioscrotal folds, and a urogenital sinus with perineal opening at the base or ventral surface of the phallus; Grade 5 = phallus with the appearance of a well-developed penis, associated with complete fusion of the labioscrotal folds, and a urogenital sinus and opening in the body of the phallus or balanic area.

Figure 1 - Prader's classification of grades of genital ambiguity

This classification of stages of virilization of the external genitalia from 1 to 5 that was proposed by Prader[21] for virilized girls with congenital adrenal hyperplasia and is also of great utility for describing other forms of DSD.

Initial laboratory tests

While definition of genetic gender is not alone a sufficient basis on which to take decisions on gender of rearing, it is of fundamental importance for guiding laboratory investigations. Karyotype testing also makes it possible to detect numerical or structural abnormalities in sex or autosomal chromosomes, in homogenous or mosaic karyotypes (more than one lineage of somatic cells in a single individual originating from the same genetic source), and also the presence of chimera (more than one lineage of somatic cells in a single individual originating from different genetic sources). Sex chromatin tests (X and Y) should not be used as a substitute for karyotype testing, due to the possibility of false positives and negatives inherent in the technique and the difficulties of interpreting complex cases.[1,2,5,6,15,19,20]

Numerical or structural aberrations of the sex chromosomes and also the 46,XX/46,XY chimera result in anomalies of gonad determination and therefore their detection indicates the need to undertake gonad biopsies for diagnostic definition. Autosomal anomalies are more frequently observed in cases of multiple congenital anomalies associated with deficiencies of neuropsychomotor development and growth.[1,2,5,6,15,19,20]

In cases of GA without palpable gonads, a hypothesis of congenital adrenal hyperplasia should be investigated even before the results of karyotyping are available, since this is the principal cause of GA in newborn infants and the salt-wasting form is potentially lethal. This is generally manifest as hyponatremia, hyperkalemia, metabolic acidosis and hypovolemia with onset during the second or third week of life (or even later), when the child is already at home. Since the principal cause of congenital adrenal hyperplasia is 21-hydroxylase deficiency, at the very least serum 17-OH-progesterone should be assayed in these cases and, where possible, clinical signs, weight and serum sodium and potassium levels should be assessed frequently (daily or every 2 days).[1,2,5,6]

Hormonal tests and karyotyping should be performed at specialist services, as should imaging of uterus, gonads, prostate and urogenital sinus, which is necessary, but not always conclusive.[1,2,5,6,15,19,20] The most often used studies are ultrasound in association with genitourinary imaging (or retrograde voiding cystourethrography) and, less frequently, computerized tomography or magnetic resonance imaging of the pelvic region.[22,23] Laparoscopy is being used with growing frequency and offers greater precision; whenever possible it should be used in association with intraoperative cystoscopy, which provides important information on the presence or absence of the urogenital sinus.[24,25]

Etiologies

There are a variety of DSD classifications in the literature, since the criteria used to group varieties of anomalies are very much heterogeneous.[6,15,19] As a consequence of the enormous complexity of this subject, all of these systems can be questioned along some lines or another. Even the most recent classification of SDA, carried out by a group of researchers with experience in the subject – the Chicago Consensus – did not entirely eliminate problems with terminology and it was not possible to completely rule out a certain degree of stigmatization. In the first instance, the suggestion of including the karyotype in the name of the disease erroneously assumes that patients do not know what it means to be 46,XY or 46,XX. While this discussion about nomenclature is welcome, the search should be continued for terms that are truly neutral and do not have connotations of a sex that may not agree with the sex chosen for an actual patient. Nevertheless, the suggestion made in the Chicago Consensus that the term intersex be replaced with DSD was unanimously accepted.[2]

Some of the most common etiologies of DSD are listed below.

The classic form of congenital adrenal hyperplasia due to 21-hydroxylase deficiency (DSD – 46,XX – fetal – 21-hydroxylase) is one of the principal causes of DSD and the most frequent cause of virilization (around 80 to 90% of cases) of fetuses with female genetic gender (46,XX). It can manifest in one of two clinical forms, simple virilization (SV) or salt-wasting (SW). The SV form accounts for 20 to 30% of cases and causes GA in female newborn infants; when untreated it leads to progressive postnatal virilization in both sexes, with signs and symptoms of early pseudopuberty (increased size of clitoris, increased size of penis without corresponding testicular growth, pubarche, hirsutism, acne, deepening of the voice, increased velocity of skeletal maturation and growth). In the SW form, which accounts for 70 to 80% of cases, the clinical manifestations include, in addition to the prenatal virilization of females and postnatal virilization of both sexes, a range of forms, from the severe cases of hyponatremic and hyperkalemic dehydration, vomiting, metabolic acidosis, hypovolemic shock and death, if treatment is not given, to more discrete cases in which reduced weight gain, abnormal electrolytes and increased plasma renin activity are the only findings. In these cases, there is a risk of dehydration and shock if children are subjected to situations of stress without appropriate glyco and mineralocorticoid treatment.[1,2,5,6,15,19,20]

Among the causes of GA in fetuses whose genetic gender is male (46,XY), partial androgen insensitivity (DSD – 46,XY – partial androgen insensitivity) and 5α-reductase deficiency (SDA – 46,XY –5α-reductase deficiency) are of prominence

and, at birth, they manifest as varying degrees of micropenis, hypospadia and cryptorchidism, and are, therefore, practically indistinguishable by clinical methods, as are other causes of virilization deficiency in male fetuses. The definitive diagnosis is frequently dependent on extensive laboratory assessments.[1,2,5,6,15,19,20] At puberty, partial androgen insensitivity is characterized by gynecomastia and little genital virilization and body hair, whereas, with 5α-reductase deficiency there is genital virilization, although not always with adequate penile growth, absence of gynecomastia and hypoplasia or absence of the prostate.[26]

Finally, among the causes of GA that are linked to gonadal disturbances, partial gonadal dysgenesis (DSD – 46,XY – partial gonadal dysgenesis) and true hermaphroditism (or ovotesticular DSD) stand out. Partial gonadal dysgenesis is characterized by the presence of the 46,XY karyotype, without mosaicism, in individuals with partial testicular differentiation or dysgenetic gonads, evidence of Müllerian duct remnants and GA without clinical signs of Turner syndrome. True hermaphroditism is also a histological diagnosis; characterized by the presence of ovarian tissues (with follicles) and testicular tissues (with seminiferous tubules, with or without spermatozoids) in a single individual, whether in one gonad (called ovotestis) or in opposite gonads.[1,2,5,6,15,19,20]

Gender of rearing

In the great majority of cases, sex is correctly diagnosed at birth without any difficulty, on the basis of the characteristics of the external genitalia alone. In normal situations there is concordance between external and internal genitalia (external and internal genital gender), gonads (gonadal gender) and sex chromosomes (chromosomal gender). Hormone production (endocrine gender) plays a fundamental role both after puberty, when individuals develop secondary sexual characteristics and reproductive capacity, and during fetal development.[27] Finally, the concordance between chromosomes, gonads, internal and external genitalia and hormone production may become compromised if there is no corresponding psychological self-identity (gender identity). Furthermore, account must be taken of social insertion into one or other gender (gender role).[1,2]

However, in pathological situations, the diagnosis of sex can only be arrived at when other data are taken into account. Faced with a child with GA, the primary objective is precise diagnosis of the etiology of the disorder, which in turn allows for correct definition of sex,[1,2,28] estimation of the risk of gonadal malignancy and the correct time for gonadectomy (when indicated),[29-31] definition of the time and type of reconstructive genital surgery,[32] prediction of spontaneous development of secondary sexual characteristics,[26] the need for replacement or substitution therapy, the chances of future fertility[33,34] and, finally, genetic counseling and psychological and psychotherapeutic follow-up of the patient and their family.[35-37]

Sociocultural, legal and ethical aspects

There is evidence that definition of gender of rearing and acceptance of sexuality differs significantly between different societies and cultures, whether in terms of social, cultural or religious aspects. In the majority of societies, the social and economic position of men differs from that of women to a significant extent, and in these cases, male gender appears to offer better life chances. The cultural baggage that physicians bring to cases can also influence the decision on gender of rearing, which emphasizes the importance of a multidisciplinary team.[38] Therefore, the discussions with the family for deciding on gender of rearing should not omit to cover the social, cultural, ethnic and religious aspects of the family or the society in which it lives.[38,39]

From the legal point of view, in Brazil the Federal Medical Council (Conselho Federal de Medicina, Resolution no. 1664 of May 2003) establishes, in Article 2, that "patients with DSD must be assured early investigation with view to appropriate definition of gender and treatment in good time." Still according to the Federal Medical Council, Article 4, "it is a requirement that there be the minimum infrastructure necessary to perform hormonal and genetic tests and imaging and pathology studies. In order that the child's final sex can be defined and assumed, it is obligatory that a multidisciplinary team exist ensuring knowledge in the areas of pediatrics, pediatric endocrinology, genetic endocrinology, child psychiatry and surgery." It is, therefore, a legal requirement that the assessment environment guarantees safety and support during care. Nevertheless, it is not every hospital that is able to provide professionals with experience in this area.

The family has every right to medical and legal assistance, support and information on the problem and their consequences throughout the assessment process. Depending on their age and ability to understand, the patient can also contribute to defining their own sex. It has been determined by the Federal Medical Council that "at the point that final gender is defined, family members or legal guardians and, possibly, the patient must be duly informed to the extent that they participate in the decision on the treatment proposed."

If a request is made to revise the legal name and sex of a child who already has a psychological and social identity or for an adolescent, this process requires profound and detailed assessment by several professionals. It is of fundamental importance that the family and, when possible, the interested party (the patient), take part in the decision on gender of rearing and on programming treatment, especially the adequate time(s) for corrective surgery. This is generally a long process that demands much cooperation of the patient and dedication of the medical team. It is now believed that certain records can be altered, if these changes are made for the true social and psychological integration of patients.

It is important to mention that, during recent years, a movement lead by societies of patients with DSD has been

fighting hard against the practice of some physicians or medical teams of taking unilateral decisions that define gender of rearing and the treatment given for GA. This becomes more relevant when the decisions are taken without providing complete information to patients' families and where surgical interventions were made early and were definitive. In the current ethical context these decisions must be completely shared with patients' families (or the patients themselves, when possible). The family must be given all of the information available and also as much time as necessary to take part, together with the medical team, in the definition of gender of rearing and planning of surgical correction of the genitalia.[40-44]

Final comments

Although DSD with GA are relatively rare in the population and rarely observed in the daily practice of pediatricians, their early and correct diagnosis requires adequate medical attention in order to make it possible to establish prognosis (puberty, fertility and malignancy), therapeutic planning and genetic counseling. This greatly reduces the anxiety of the family and the risk of psychological and social problems. A multidisciplinary team working at a tertiary service is of fundamental importance to diagnostic and therapeutic success. The pediatrician is a key player in this team, since they will often be responsible for providing the first information to the family and should assume the role of intermediary between them and the multidisciplinary team, respecting their particular social, cultural, economic and religious characteristics.

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