Residência Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria
ISSN-Online: 2236-6814

Submitted on: 02/14/2021
Approved on: 04/06/2021

ORIGINAL ARTICLE

Cases of ambiguous genitalia from a public university hospital

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Keywords:
Disorders of Sex Development, Karyotype, Genitalia.

Abstract

Objective: Ambiguous genitalia is a disorder of sex development. Incidence has been estimated at approximately one in 4,500-5,500 live births. The investigation and diagnosis of ambiguous genitalia is a clinical emergency given the importance of detecting life-threatening conditions such as congenital adrenal hyperplasia and malformation syndromes early on. **Method:** This cross-sectional observational study included 56 medical charts of patients referred to the Pediatric Endocrinology Department of a public university hospital. **Results:** Congenital adrenal hyperplasia was the most common disease with 11 cases (19.5%), followed by partial androgen insensitivity syndrome with eight cases (14.2%), Klinefelter syndrome with five cases, and mixed gonadal dysgenesis with four cases. Patient mean age at first visit was 55 months. Family history, gestational history, gonadal characteristics, and treatment were also analyzed. **Conclusion:** The identification and management of children and adolescents with ambiguous genitalia must be carefully executed by a multidisciplinary team with experience on the subject. The repercussions of late diagnosis or inadequate case management cannot me measured, but affect the way patients relate to themselves and society around them.

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Residência Pediátrica; 2022: Ahead of Print. DOI: 10.25060/residpediatr-2022.v12n4-560

INTRODUCTION

According to the 2006 Chicago Consensus, disorders of sex development (DSD) are defined as: (1) obvious ambiguous genitalia; (2) apparently female genitalia with clitoromegaly, posterior labial fusion, or inguinal/labial mass; (3) apparently male genitalia with bilateral cryptorchidism, micropenis, isolated perineal hypospadias, or moderate hypospadias with cryptorchidism; (4) family history of DSD; (5) discordance between genital appearance and prenatal karyotype[1].

There are no clear estimates of the incidence of ambiguous genitalia at birth, as only a proportion of individuals with this condition present difficulties with sex designation. However, incidence has been estimated at approximately one in 4,500-5,500 live births[2].

The global incidence of individuals with karyotype 46,XY and DSD has been estimated at 1:20,000 live births. Ovotesticular DSD occurs in 1:100,000 live births[3]. The incidence of 46,XX DSD primarily consisting of congenital adrenal hyperplasia (CAH) has been estimated at 1:14,000-15,000 live births[4,5].

In general, suspicious cases are picked up by an assisting pediatrician assistant, either in the delivery room or in routine consultations. Especially when performed in the neonatal period, investigation and diagnosis of ambiguous genitalia constitute a medical emergency. This is due to the importance of early detection of life-threatening conditions such as CAH and malformation syndromes. This is a situation that causes intense stress in parents, since they must choose the child's sex of rearing[6].

In suspected cases, it is essential that investigation be carefully conducted with the support of a multidisciplinary team at a referral center. In this process, acquiring the patient's medical history and performing careful physical examination are required in diagnostic investigation.

Interviews with patients and parents must include an assessment of pregnancy history, with special attention to the use of medication and signs of maternal virilization during pregnancy and cases of low birth weight. It is also important to ask actively about family history, such as consanguinity between parents, similar cases in the family, family history of delayed or precocious puberty, infertility, hypertension in childhood, or unexplained deaths in the first months after birth[7].

The external genitalia must be evaluated for degree of virilization, considering the following: phallus size; position of the urinary meatus; presence of a vaginal introitus or opening of the urogenital sinus; degree of fusion, symmetry, pigmentation and rugation of the labio-scrotal folds; presence of inguinal masses; and the location and size of the gonads[7].

The Prader scale was initially designed to assess the degree of secual ambiguity in individuals with CAH. However, in clinical practice it is often used in other cases of ambiguous genitalia (Figure 1).

Inguinal gonads can be detected by palpation and ultrasonography (US). US examination also identifies intra-abdominal gonads, the uterus, and adrenal abnormalities. However, the ability of US to locate intra-abdominal ovaries and testes is limited and may require supplementation with other imaging modes, such as nuclear magnetic resonance (NMR)[9].

METHOD

This cross-sectional observational study looked into the medical charts of individuals referred to the Pediatric Endocrinology Department of a public university hospital, with children referred from the General Pediatrics Outpatient Clinic of the same hospital and from other public hospitals and clinics in the State of Rio de Janeiro. Ours is a teaching outpatient clinic, also a member of the Brazilian Unified Healthcare System, which provides primary and secondary care to low-income children from birth to 11 years of age. This study was approved by the Research Ethics Committee and given certificate no. 34116420.9.0000.5259.

We included children and adolescents aged 0-17 years diagnosed with ambiguous genitalia at the first consultation, according to criteria established in the 2006 DSD Consensus[1]. Individuals diagnosed with panhypopituitarism or constitutional delay of growth and puberty were excluded. This study was approved by the Ethics and Research Committee of the institution.

The medical records of 56 individuals were eventually selected. They were analyzed for the following criteria: age at first consultation; age of civil registration; gestational history; family history; presence of consanguinity; imaging scans; karyotype; social gender; concordance with genetic sex; and change of sex in civil registration documents. The following were analyzed in the documentation of physical examination at the first consultation: description of the genitals; application of the Prader scale; presence of palpable gonads; laterality of the gonads; and dysmorphisms or congenital malformations. The last items considered were diagnosis and proposed treatments.

Significant elements in family history were the presence of first-degree relatives with an established diagnosis of DSD or a history of ambiguous genitalia. Consanguinity was defined as any degree of kinship between the parents. Gestational history findings included any complications and use of medication during pregnancy.

Performed imaging exams included US scans of the abdomen, pelvis and labioscrotal swellings, besides MRI scans of the abdomen and pelvis, as needed in the investigation of each case.

Karyotyping tests were performed in different laboratories, with most samples analyzed in the institution's Cytogenetics Laboratory.

Social gender was defined as the sex assigned to the patient in their civil registration documents.

The Prader scale was used to categorize patients based on the degree of genitalia virilization. A micropenis was defined as a phallus measuring less than or equal to -2.5 standard deviations (SD) for age and ethnicity[10].

The gonads were described as palpable or non-palpable and as located on the labioscrotal swellings or inguinal region. In cases where the gonad was palpable, laterality was established as right or left.

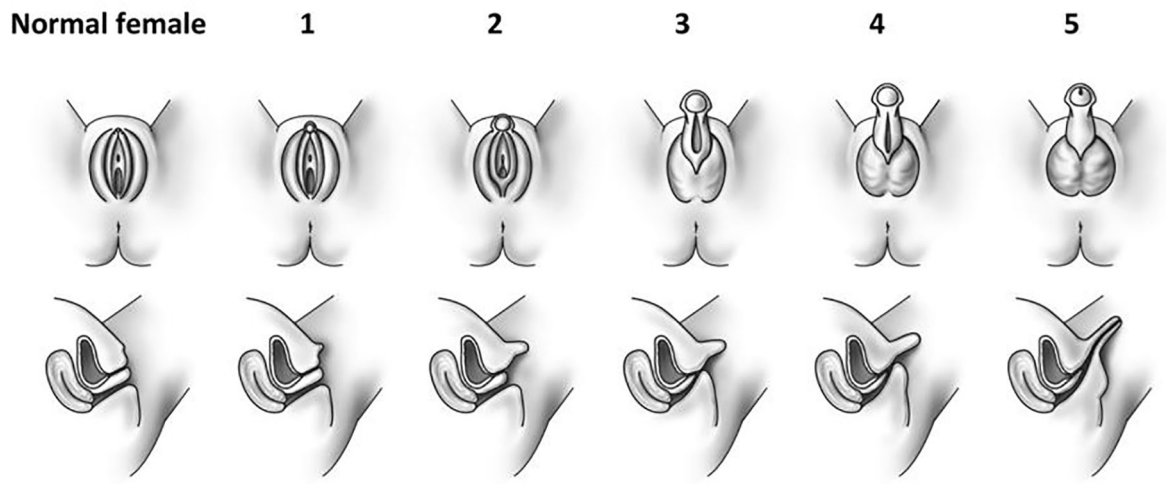

Figure 1. Representation of Prader's classification of the external genitalia of patients with congenital adrenal hyperplasia according to degree of virilization8

The collected data were processed and analyzed on Excel for Windows version 8.0 (Microsoft Corporation; Redmond, WA, USA).

After compiling the data, we calculated the mean values of continuous variables and the frequencies of categorical data.

RESULTS

We analyzed 56 medical charts of patients diagnosed with ambiguous genitalia at the first visit seen at the service between the years of 2010 and 2020. The most common diagnosis was CAH with 11 cases (19.5%), seven of which were of the salt-wasting form. The second most common diagnosis was partial androgen insensitivity syndrome with eight cases (14.2%), followed by Klinefelter syndrome (five cases) and mixed gonadal dysgenesis (four cases). Diagnostic assessment was not concluded in 18 cases (28.5%), for reasons such as treatment abandonment and non-availability of specific molecular tests.

Table 1 shows the frequencies of the different diagnoses from the initial presentation of ambiguous genitalia.

The mean age at first visit was 55 months. Only 11 individuals had their first visit within 12 months of birth, and only eight in the neonatal period. Conversely, eight individuals were aged 12 years or older at the first visit. At the time of admission to our service, 46 patients with ambiguous genitalia (82.1%) had an established social gender. The mean age of civil registration was 1.21 months.

Almost half (46.2%) of the patients had a 46,XY karyotype and 25% were 46,XX. In addition, five patients had karyotypes with chromosomal aberrations, four were 47,XXY and one was 48,XXXY. Eight individuals were lost during follow-up and did not undergo karyotyping.

The male social gender was chosen in 33 cases (58.9%) and the female in 23 (41.1%). In eight cases (14%) there was discordance between the social gender and the genetic sex. Two individuals had their sexes changed in civil registration documents.

Physical examination records indicated that 30 patients (53.5%) had palpable gonads. Bilateral gonads were seen in 25 individuals. Table 2 shows the distribution of patients based on the Prader staging with their respective frequencies. Three subjects (5.3%) were not categorized since adequate characterization of the genitalia was not performed.

Table 2 shows the distribution of individuals according to the Prader staging at the first visit to our service.

Seven individuals presented associations with congenital malformations, with kidney malformations ranking as the most frequent (four cases).

Table 3 summarizes the main characteristics observed in individuals with DSD seen at the Pediatric Endocrinology Department.

As shown in Table 3, six individuals had first-degree relatives with CAH and DSD. Another three individuals had a family history suggestive of DSD, with reports of relatives with micropenis, genital surgery, and infertility. Only two of all patients presented a history of parental consanguinity.

In gestational history findings, the most common occurrences were hypertension and gestational diabetes mellitus with nine and five cases, respectively.

Six individuals had at least one other malformation, with kidney malformation as the most common with four cases. Fifty individuals (89.2%) had no other associated malformations.

In terms of treatment, 21 individuals underwent surgery. Eleven underwent genitoplasty, three underwent hypospadias repair, and six underwent inguinal hernia repair with gonad biopsy.

DISCUSSION

Cases of ambiguous genitalia require careful assessment and the involvement of a multidisciplinary team including pediatricians, endocrinologists, surgeons,

Table 1. Frequencies of the different diagnoses of DSD* from the initial presentation of ambiguous genitalia

Final diagnosis	N	Prevalence (%)
Congenital adrenal hyperplasia	11	19.5
Klinefelter syndrome	5	8.9
Mixed gonadal dysgenesis	4	7.1
Complete androgen insensitivity syndrome	3	5.3
Partial androgen insensitivity syndrome	8	14.2
Ovotesticular DSD	3	5.3
46,XY DSD secondary to a diagnosis of syndrome	1	1.7
Kallmann syndrome	1	1.7
Isolated genitourinary malformation	2	3.5
Indeterminate diagnosis	18	32.1

* The acronym DSD refers to disorders of sex differentiation.

Table 2. Distribution of individuals according to the Prader staging

Prader stage	n	Prevalence (%)
1	6	10.7
2	2	3.5
3	14	25
4	17	30.3
5	14	25

Table 3. Characteristics of individuals with DSD* seen at the Pediatric Endocrinology Department of a public university hospital

Characteristic	n(%)	Characteristic	n(%)
Family history		**Concordance with genetic sex**	
Congenital adrenal hyperplasia	4 (7,1%)	Yes	39 (69,6%)
Diagnosis of DSD	2 (3,5%)	No	8 (14%)
Diagnosis of micropenis	1 (1,7%)	Investigation not concluded	9 (16%)
History of genital surgery	1 (1,7%)		
History of infertility	1 (1,7%)	**Presence of other congenital malformations**	
		One	3 (5,3%)
Consanguinity		Two or more	3 (5,3%)
Yes	2 (3,5%)	None	50 (89,2%)
No	43 (76,7%)	**Karyotype**	
No information in medical charts	11 (19,6%)	46,XY	26 (46,4%)
		46,XX	14 (25%)
Gestational history		47,XXY/48,XXXY	5 (8,9%)
Hypertension during pregnancy or before	9 (16%)	Mosaic	3 (5,3%)
Gestational diabetes mellitus	5 (8,9%)	No karyotyping	8 (14,2%)
Premature placental abruption	2 (3,5%)		
Use of licit or illicit drugs	2 (3,5%)	**Surgery**	
Attempted induced abortion	2 (3,5%)	Genitoplasty	11 (19,6%)
Signs of maternal virilization	1 (1,7%)	Inguinal hernia repair	6 (10,7%)
		Hypospadias repair	3 (5,3%)
Sex of rearing			
Male	33 (58,9%)		
Female	23 (41%)		

* Disorders of sex differentiation

geneticists, psychologists, and social workers, to name a few. Since this is a complex condition, it should preferably be treated in referral centers.

As recommended, the sex of rearing must be determined as early as possible after careful assessment, given the stressful nature of the situation experienced by patient families[5]. In our population, we found that 82.8% of the individuals were registered with a defined sex of rearing, despite the presence of ambiguous genitalia and the lack of adequate team assessment. In these cases, the designation of the sex of rearing was hasty and sometimes inappropriate.

Mean age at first visit was 55 months, which was lower than in another similar case study in Thailand, where the mean age at first visit was 80 months[11]. The authors found that 22 of 95 patients had been evaluated before reaching one year of age[11]. In a study carried out in another Brazilian referral

center, 50.6% of the patients with ambiguous genitalia were seen in the first year of life, showing that even in other centers there still is delay in referrals[12].

Despite the earlier age at first visit seen in our service compared to other studies, the evaluation of a newborn with ambiguous genitalia should be initiated in the neonatal period[11,12]. The importance of early assessment lies on the identification of potentially serious conditions such as CAH, and allows families to mode adequately define the child's sex of rearing.

Multidisciplinary follow-up is an important element in the continuity of comprehensive care. Eighteen individuals were lost during follow-up before a diagnosis was reached, which may indicate the need to expand follow-up efforts involving the individual and their family into mental health and social services while improving doctor-patient communication, and addressing the socioeconomic issues present in this context. Losses during follow-up or adoption of inadequate approaches results in psychosocial disturbances that may affect patients throughout their lives.

Our findings stressed the need for greater availability of molecular biology tests in public healthcare services, making it possible to speed up diagnosis, increase diagnostic accuracy, and positively impact the choice of approach. Proper diagnosis allows more accurate definitions around prospects of spontaneous puberty, fertility, and choice of sex of rearing.

Physical examination records showed that 45 individuals had significant ambiguous genitalia with Prader degrees between III and V. It is important to note that in Prader degree V, the genitals have a male aspect but do not present palpable gonads, since this classification was proposed for girls virilized by CAH; nevertheless, given its easy-of-use, the Prader scale has been employed more widely. In our series, 53.5% of the patients had palpable gonads. We also saw that gonads could be testicles, ovaries or ovotestes. Therefore, this data should be interpreted cautiously to avoid inappropriate designation of sex as male.

The most common cause of ambiguous genitalia is CAH, although this is not the only context in which this condition presents itself[8,9,11]. CAH must be considered in individuals with apparently male genitalia and no palpable gonads.

Surgery is controversial and several approaches have been discussed. The decision and timing of genital surgery should take into consideration the family's decision with the support of the multidisciplinary team. Functional issues regarding the individual's sexuality and future fertility must also be considered. Much has been discussed about patient autonomy in this decision and the applicability of this idea in the pediatric age group. To date, there is no consensus on exactly when and how this decision should be made. However, there are recommendations that definitive interventions should be postponed until the individual can participate in decision-making and provide consent.

CONCLUSION

The identification and management of children and adolescents with ambiguous genitalia should be carefully conducted by an experienced multidisciplinary team. The repercussions of late diagnosis or inadequate case management cannot me measured, although they affect the way patients relates to themselves and society around them. Therefore, it is essential that pediatricians be aware of this diagnostic possibility and advise patients to seek care at a referral center.

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