

Disorders of Sex Development: Ambiguous Genitalia and Partial Androgen Insensitivity Syndrome

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Abstract

Background – Disorders of sex development (DSDs) also known as “intersex” are congenital conditions in which chromosomal, gonadal, and anatomical development mismatch. One in 4,500 infants is born with abnormalities of external genitalia, which are mostly unexplained in molecular terms. Androgen insensitivity syndrome (AIS) is a common cause of DSDs.

Objective – One of the three broad subdivided phenotypes of AIS are partial androgen insensitivity syndrome (PAIS). Feminization (i.e., undermasculinization) of the exterior genitalia at birth, secondary abnormal secondary sexual development at puberty, and infertility in individuals with 46, XY karyotype are the proof. In males, PAIS is common to observe a micropenis, hypospadias, and cryptorchidism. Women who have clitoromegaly and fused labia during puberty are characterized as individuals with PAIS.

Case – We reported a 13-year-old child with the chief complaint of primer amenorrhea. The patient was a girl but not yet got her menstruation. Patient was referred by a Endocrinology Fertility and Reproductive Consultant of OBGYN who had done chromosomal and hormonal analysis. We performed a laparoscopic explorative study where we did not find uterus, fallopian tubal, and ovaries. But, we found testis in the inguinal canal.

Conclusion – Decisions regarding gender assignment are still confronted between patient’s family and medical staff. The ambiguity of genital, physical, and psychosocial adjustment for sex assignment can determine the prognosis.

Keywords Disorders of sex development, ambiguous genitalia, partial androgen insensitivity syndrome, laparoscopic explorative, intersex

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1. Introduction

Ambiguous genitalia is an anatomical appearance form of disorders of sex development (DSDs), and this term is used to describe the mismatch in the development of chromosomal, gonadal, and anatomical forms (Michala et al., 2013). It has been estimated that about 1 in 4,500 infants is born with ambiguous genitalia and mostly of cases unexplained in molecular terms (Ancher mann, 2014). 46, XY is one of the three subdivided DSDs which often anatomically appear as ambiguous genitalia. Androgen insensitivity syndrome is a common cause of DSDs (Ainsworth, 2015). Various types of imaging such as ultrasonography and magnetic resonance imaging are required to diagnose DSD, via chromosomal, biochemical, and endocrinological examination. Laparoscopy is widely accepted as a tool to diagnose DSD and also to treat DSD because of its minimal invasiveness (Moriya *et al.*, 2014).

Appropriate management can be challenging in most cases, and we need a collaborative multidisciplinary approach with appropriate expertise. General management of infant with DSD should include the following: gender assignment, place in evaluating and managing is a centre with multidisciplinary team, and communication to the parent of the infant for contribute to decision making (Woodward and Neilson, 2013). Physiological care throughout life is also essential. The ambiguity of genital, physical, and psychosocial adjustment for sex assignment can determine the prognosis (Mendoza and Motos, 2013).

In recent years, the scientific drive in the field of DSD has focused on identifying new gene variations (mutations) that lead to atypical sex development. There is often then a time lag between such genetic discovery and routine genetic screening with larger populations. Now that automated gene sequencing is available in many biochemistry departments; however, the identification of genetic variations as part of a routine medical work up is becoming more common. The next phase of development of our knowledge base for DSDs will be in identifying subtleties of physical health characteristics and long-term physical health risks of each genetic group (Bashamboo *et al.*, 2010).

Some individuals with a DSD diagnosis may find genetic research an esoteric subject with little relevance for their well-being. However, the scientific agenda is often driven by pertinent medical issues. First of all, there are families with several members who have a DSD diagnosis and these families may also have individuals who carry a variant gene or a group of variant genes. This topic is currently especially relevant to those diagnoses that are associated with male-typical XY (sex) chromosomes. Individuals with these diagnoses present to a greater or lesser extent male-typical physical sex characteristics, such as a significant amount of facial and body hair, enlargement of the clitoris, and deepening of the voice. Second, it may be possible to identify patterns of health concerns that could affect long-term follow-up once we know how to differentiate one condition from another at the genetic level.

Rather than going into the detail of each new genetic variant in the physical sex differentiation pathway, this overview will discuss the common conditions that come under the heading of DSD and then review the advances that affect medical management derived from experience in a tertiary multidisciplinary DSD clinic. Scientific progress will also be promoted by the increasing popular strategy of collaborating groups of clinicians combining knowledge of larger cohorts of individuals with DSD diagnoses so that long-term outcomes can be documented. As DSDs are rare conditions, it is important to construct larger cohorts so that the spectrum of variability on each condition can be documented. An international collaboration entitled iDSD is one such initiative. This work will allow for greater confidence and speed of diagnosis for new cases as they arise (Ludbrook and Harley, 2011).

Outcome studies on the psychological well-being of individuals with DSD have tended to focus on the group with congenital adrenal hyperplasia (Idris, 2014). Among those with 46,

XY DSD, the largest group studied has partial androgen insensitivity syndrome (PAIS). A long-term follow-up study of adults with PAIS found that there is increased psychological distress in this group, as determined by responses to the Brief Symptom Inventory (BSI). While it is clear that some individuals with PAIS experience psychological distress, it is as yet unclear which subpopulation is most at risk. Outcomes of mental health in girls and women affected by complete androgen insensitivity syndrome (CAIS) vary greatly across studies. For example, psychological distress, self-harming behavior, and suicidal tendencies are prevalent in some samples of women with CAIS recruited via physicians or support groups. Similar patterns of psychological distress have been identified from responses to the BSI, and suicidal ideation has been observed in 46, XY women with 5-alpha reductase deficiency and 17-beta hydroxyprogesterone deficiency (Wisniewski, 2009).

The management of DSD is complex and has undergone major shifts in the last decade. The initial approach was to apply the "optimal gender policy" whereby the primary thrust of the management was to normalize the physical appearance in line with the gender of rearing (Thyen *et al.*, 2014). Thus, early constructive surgery was advocated. However, after reviewing reports from patient advocacy groups and clinicians, there are recommendations to postpone any corrective surgery until the child is able to give consent (full consent policy), although not all clinicians agree with this policy (Wiesemann *et al.*, 2010). It is thus imperative to assess psychological outcomes of these patients to allow for evaluation of management policies which can then guide future clinical practice guidelines.

2. Case presentation

A 13-year-old child came to the gynecology polyclinic with a chief complaint of no menstruation. Patient was referred by the OBGYN consultant and had undergone chromosomal assessment. Her breasts have no enlargement but pubic hair was present normally. In sex organ, she complained there is something like a penis that became bigger and bigger by the time. She urinates not from the penis but from the hole under the penis.

In the physical examination, we get normal condition and assess the gynecological status and get breast in M2 and pubic hair in tanner IV. In genital, there are presence of labia mayora and also a phallus-like penis. We also assessed ostium uteri and get no ostium uteri externa.

Patient had undergone chromosomal analysis and the result is 46, XY chromosomal with no major defect. Clinical variant individual with 46, XY DSD are disorders of testes development and disorder of androgen sensitivity. Patient was suggested to undergo hormonal examination, analysis gonad function by HCG value, radiology examination or laparoscopy for internal genitalia, DNA examination, and consult a endocrinology pediatric consultant and also with DSD team.

In the hormonal examination, the results were HCG <2 mIU/ml, LH 4–18 mIU/ml, FSH 12–13 mIU/ml, estradiol <20 pg/ml, and also testosterone 666.3 ng/ml. We performed a laparoscopic explorative where we did not find a uterus, fallopian tubes, and both ovaries. But, we found testes in the inguinal canal.

3. Discussion

Primary amenorrhea, clitoromegaly and woman with a male karyotype are the clinical presentation in 46, XY DSD patients due to androgen insensitivity syndrome (Mendoza and Motos, 2013). This patient is assigned as a woman but has a phallus-like penis with 46, XY karyotype. Androgen insensitivity syndrome is the common cause of DSD. The pathogenesis of 46, XY DSD may or may not be related to endocrine dysfunction. Non-endocrine disorders result from the abnormal development of urogenital primordia.

Endocrine causes can be further categorized into impaired or absent androgen production or specific androgen receptor or post-receptor dysfunction in target organs. Normal development male genitalia requires the production of fetal androgen as well as functioning receptors.

Hormonal assessment in this patient shows decreasing in estradiol and increasing in FSH level, and high testosterone level. Well-trained multidisciplinary teams are required for management in patients of 46, XY DSD. Important to good outcomes of patients require early diagnosis. In the treatment of DSD patients require psychological evaluation. For this patient we have done chromosomal analysis and also performed laparoscopic explorative to diagnose asses genitalia internal.

4. Conclusion

Long-term outcomes for DSD patient is difficult to quantify, and proper management and adjustment assign of sex will influence the prognosis of DSD.

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