Overview on sex determination and Sexual ambiguity (part 1)

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Abstract
Alfred Jost (1974) showed that all mammalian embryos naturally resulted in female offspring; therefore, to produce male offspring, some factors need to intervene in this natural process.
The SRY gene differentiates the genital ridges to the testis. The testis secretes two essential hormones: anti-Mullerian factor inhibits the growth of the Mullerian system and testosterone initiates the growth of the Wolffian duct and converts the urogenital sinus to male external genitalia. Any error in this long and complicated process results in ambiguous genitalia which could be minor or major according the severity of the error. In 2005, the results of the errors were termed “Disorders of Sex Development (DSD)” which includes a vast range of ambiguities in human genital that are classified according to the etiology:
I. Sex chromosomal aberrations
II. Gonadal dysgenesis
III. Enzyme defects (under or over expression)
IV. Anatomical abnormalities
We will discuss them more in the following issues of Genetics in the 3rd Millennium.

Keywords: Gonadal ridges; Sex Determination; Sexual ambiguity, Disorders of Sex Development; SRY Genes;

Introduction
Alfred Jost, the French Physiologist (1974) (1), in some magnificent experiments, showed that all castrated rabbit embryos, before sex differentiation, produced female offspring regardless of the chromosomal constitution (2). Male gonads and their essential hormones, i.e. anti-Mullerian factor to inhibit Mullerian development and testosterone to initiate the Wolffian growth and convert the urogenital sinus to male external genitalia (3), are required to produce a male embryo.
He also delineated that if a piece of the rabbit testis was transplanted to embryos with female chromosomal karyotypes whose gonads were to differentiate into ovaries, the differentiation process changed to produce the testes. He reached the conclusion that all embryos naturally produced female offspring regardless of the chromosomal constitution (2-3)

Development of the reproductive organs
In the early gestational age, accumulation of coamomic epithelium and mesenchymal cells beneath the coamomic cavity on the lateral sides of the midline in the back produces genital ridges. The genital ridge is undifferentiated at the beginning until 8 weeks gestation. In this period, the only way
to differentiate the male and female gonads is to analyze X or Y body of the cells. At 7 weeks, gonadal differentiation starts and continues until 16 weeks gestation (4, 6,7).

In male chromosomal constitution, the SRY gene guides the genital ridges toward differentiation to the testis.

The testis produces two essential hormones: anti-Mullerian factor, which inhibits the Mullerian development process, and testosterone, which is the main product for stimulating the Wolffian duct in the developmental process. The Wolffian duct produces the vas deferens, epididymis, and seminal vesicle, and the Mullerian system regresses. The only remnant is a part of the prostatic urethra (4,5,7).

In female embryos, the Mullerian duct grows longitudinally down and fuses with the ipsilateral duct in the midline. The proximal part produces the fallopian tubes and the distal part produces the uterus, cervix, and upper one third of the vaginal canal. The Wolffian duct regresses except for some remnants along the uterus, cervix, and vaginal wall.

The cortical part of the genital ridges produces the cortical part of the ovary while the central part produces the ovarian medulla. In the male embryos, the cortical part forms tunica albuginea and the medial parts produce the seminiferous tubules (4,9).
The Process of Reproduction

Although reproduction is a continuous process, it could be divided into four phases (10, 11):

1. Differentiation of genital ridges to the ovary or testis according to the chromosomal constitution of the embryo.
2. Development of Mullerian/ Wolffian duct, forming the female or male internal genitalia.
3. External genitalia such as gonads have a unique origin including the genital tubercle, genital fold, and labioscrotal fold, which form the clitoris, minor, and major labia in the female or glans, shaft, and scrotum in the male embryo, depending on the gonadal hormone, respectively.

It has been shown that sex determination and sex differentiation is a very lengthy and complicated process. If all steps are taken properly, the result is a anatomically normal male or female neonate; otherwise, minor or major abnormalities may be observed depending on the severity of the errors.

These malformations usually cause sexual ambiguity and trouble in the sex assignment, especially in adults. The sexual ambiguity comprises a variety of physical and anatomical changes that render its classification very difficult.

One of the most challenging problems in neonatology is sex assignment (10-12) for an ambiguous neonate, which requires the cooperation of a team of specialists including a neonatologist, a geneticist, an endocrinologist, and a psychiatrist.

When all steps are taken properly, the result will be a normal male or female neonate in whom sex assignment is very easy. However, if an error occurs during this long and complicated process, it may result in abnormalities in sexual organs. Depending on the severity of the error, the abnormality could be minor, such as cliteromegaly in girls or mild hypospadias in boys, or major such as severe changes in the internal and external genitalia (13) toward the opposite sex. These diversities, such as maldevelopment of internal and external genitalia or both, cause confusion in sex assignment; therefore, it has been termed intersex, meaning a mixture of both sexes. Theodore Klebs (1876) classified this phenomenon into 3 categories (14-16):

- A true hermaphrodite (complete intersex) patient has to have at least one ovary containing Graafian follicles with oocytes, and one testis with seminiferus tubules. The male and female gonads could be on one side forming an ovotestis, or could be on the right and left side of the baby separately (11-13).

- Pseudohermaphroditism is a condition in which the newborn has a male or female karyotype and relevant gonads with some characteristics of the opposite sex; therefore, there are two types of pseudohermaphroditism:
  a) A male pseudohermaphrodite patient has a 46, XY karyotype and testes with some characteristics of the female phenotype.
  b) A female pseudohermaphrodite has a 46, XX karyotype and ovaries along with the signs of masculinization such as labioscrotal fusion or cliteromegaly or both. This definition and classification was acceptable and used for a long time, from 1876 until 2005 (11-13).

As these definitions bothered the patients and their families from social and legal points of view, a group of experts including neonatologists, endocrinologists, geneticists, and surgeons decided to overcome the problem in 2005 (13). They proposed the term “Disorders of Sex Development (DSD)” for all kinds of sexual ambiguity, which includes a vast range of abnormalities in terms of the frequency and outcome. There are several classifications but none of them is comprehensive and satisfactory from the clinical point of view. Recently, some authors proposed that the following classification might be more practical. They classified DSDs according to the etiology of the disease (13-20).

The proposed classification of the disorders of sex development:

I. Sex chromosomal aberration
II. Gonadal Dysgenesis
III. Enzyme defects (under or over expression)
IV. Anatomical abnormalities

DSDs are a very vast topic and we will discuss them more in the following issues of Genetics in the 3rd Millennium.
References

1. Loriaux LD. Endocrinology 2010; 20(1):1
4. Longmann’s Medical embryology.Reproductive organs 10th Ed. William and Wilkins
12. Federman DD. Abnormal Sexual Development.W.B. Saunders Co 1968
16. Sharon E. Preves 2005.Inter sex and Identity 2nd paperback print.Chapter II. Medical sex assignment 101 Inter sex
19. Developmental disorder. Wikipedia the free encyclopedia
نگاهی به تغییر جنسیت و ایهام جنسی

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چکیده/ آلفرد جاست آندروالوژیست فرانسوی بر اساس یک سری آزمایشات بر روی خرگوش به نتایج ارزش‌آمیزی دست یافت.

این دانشمند عده‌ای از جنین‌های خرگوش را قبل از تمایز جنسی اخته نمود که تمام آنها بدون توجه به ساختار کروموزومی (ژنتیک) بصورت جنین ماده متولد شدند. سپس به جنین‌های خرگوش که در حال تمایز به سوی جنس ماده بودند قطعه‌ای از بیضه خرگوش یپون خورده. ماهیت‌های کریمی نژاد که همه آنها تغییر جنسیت داشتند، به دو دسته خرد و بالا تقسیم شدند.

از مجموعه این آزمایشات به این نتیجه رسید که جنین‌های پستانداران بطور طبیعی بصورت جنس ماده متولد می‌شوند. برای اینکه جنین تبدیل به جنس نر شود لازم است عاملی بر روی این روال فعالیت داشته باشد که موجب تغییر جنسیت و جهت تبدیل خرگوش به نر شود. این حالت باعث می‌شود که جنین به جنس نر تغییر کند.

از این جنین‌ها که جنس نر و جنس دختر دارند، سولوترو بشكلی دو بویژه خرگوش نر و خرگوش ماده قرار می‌گیرد که باعث می‌شود که این جنین‌ها تغییراتی در جنسیت داشته باشند.

بر اساس دست‌آوردهای موجود در انسان، نیز این روند وجود دارد که باعث شود جنین‌ها تغییراتی در جنسیت داشته باشند.

کل، این آزمایشات به نشانه‌ای از وابستگی بین ساختار کروموزومی و تغییرات جنسیت می‌باشد. برای تولید جنس نر، ضرورت است که ژن SRY و موجب تمایز گوناد اولیه نامتایز به بیضه می‌شود. بیضه دوی، هورمونی که در سلولهای SRY قرار دارند ضروری است که باعث می‌شود که مانع رشد سیستم مولر و تبدیل آنتی‌مولرینر شود که موجب تبدیل جنسیت به جنس مرد می‌شود. هورمون دیگری تستوسترون توسط سلولهای بیضه ترشح می‌شود که موجب تغییر جنسیت به جنس زن می‌شود.

کناره‌گیری از هرکدام از این موارد به طور طبیعی ممکن است که تغییراتی در جنسیت داشته باشد.

نگاهی به تعیین جنسیت و ابهام جنسی

SRY

واژگان کلیدی: جوانه گونادی، تعیین جنسیت، ابهام جنسی، اختلالات رشد دستگاه تناسلی، ژن تغییرات جنسیت و ابهام جنسی

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