When a Woman is not a Woman: Problems and Perspectives of Congenital Adrenal Hyperplasia*

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MISCONCEPTION OF SEX AND GENDER

Not infrequently eminent athletes such as Shanti Soundarajan, Pinki Pramanik and Caster Semenya have been humiliated by questioning their sexual identity. Controversies occurred when these female athletes had high androgen levels incongruent with their sex. These tragedies were due to our misconception regarding sexes. Firstly, sex is different from gender. Harry Benjamin clarified, “Sex is what you see and gender is what you feel”. But the word ‘gender’ is often used euphemistically to mean ‘sex’ - thus adding confusion to the topic. Secondly, we tend to neatly compartmentalize sexes into male and female. In fact, sex is a spectrum. On one end of the spectrum is ‘absolute male’ and at the other end is ‘absolute female’. These absolute forms do not really exist and they are simply hypothetical. Therefore, a conventional male is a person who falls near the male end of the spectrum. Thus, he will have a majority of male attributes and a minority of female attributes. The contrary of this is also true of a conventional female. Accordingly, maleness or femaleness is determined by a group of attributes (Table 1). Although, in a given individual, these attributes are usually congruent with each other, it need not always be the case. Incongruence of the sex attributes moves an individual away from the poles of the spectrum. With increasing degree of incongruence, the person tends to fall more towards the middle of the spectrum. The more we move towards the center of the spectrum, the lesser is the degree of clarity and consensus.

Table 1: A comparison of sexual attributes

<table>
<thead>
<tr>
<th>Sex Attributes</th>
<th>Conventional Male</th>
<th>Conventional Female</th>
<th>CAH *</th>
</tr>
</thead>
<tbody>
<tr>
<td>External Genitalia</td>
<td>Penis, Scrotum</td>
<td>Vagina, Vulva, Clitoris</td>
<td>Hypoplastic Vagina, Enlarged clitoris mimicking penis, Fused labia mimicking scrotum (Male like)</td>
</tr>
<tr>
<td>Gonads</td>
<td>Testes</td>
<td>Ovaries</td>
<td>Ovaries (Female like)</td>
</tr>
<tr>
<td>Hormone</td>
<td>Predominantly androgen</td>
<td>Predominantly estrogen</td>
<td>Androgen (Male like)</td>
</tr>
<tr>
<td>Chromosome</td>
<td>46 XY</td>
<td>46 XX</td>
<td>46XX (Female like)</td>
</tr>
<tr>
<td>Psychosocial Behavior</td>
<td>Attracted to females</td>
<td>Attracted to males</td>
<td>Variable</td>
</tr>
</tbody>
</table>

*In Congenital Adrenal Hyperplasia (CAH) incongruence of sex attributes is obvious

AN INTRODUCTION TO PROBLEMS OF CAH

One such condition with a high degree of incongruence amongst the sex attributes is congenital adrenal hyperplasia (CAH). (Table 1) It is actually a group of disorders that is more common in females. In this condition, congenital deficiency of enzymes blocks the synthesis of cortisol and/or aldosterone to a varying degree, thus resulting in a spectrum of disorders. Consequent to blocked synthesis of cortisol, the pent-up precursor - pregnenolone - is diverted to produce more testosterone. (Fig. 2) Low serum cortisol, by negative feedback, increases the synthesis of adrenocorticotrophic hormone (ACTH) which in turn causes hyperplasia of the adrenal cortex and hence more production of testosterone. This vicious cycle continues until it is interrupted by medical intervention. The high testosterone level

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occuring as early as second trimester of pregnancy leads to virilization of the female fetus. Hormonal discordance in CAH causes not only metabolic derangements but also genital ambiguity. Life-long supplementation of corticosteroids will restore metabolic disturbances but not the virilized genitalia. Genital ambiguity, which almost always requires surgical correction, is extremely difficult to manage.

Figure 2: Steriodogenesis and pathogenesis of congenital adrenal hyperplasia

SURGERY OF CAH - CLITORIDECTOMY

The original aim of surgery was to neatly fit the CAH patient into one of the two misconceived sex-compartments. Feminization is technically less cumbersome and chromosomally more congruent than masculinization of a female CAH patient. For that reason, these patients are invariably assigned to female sex. The easiest way to feminize the external genitalia is to excise the enlarged clitoris which resembles a penis. In 1930s Hugh Hampton Young at Johns Hopkins University pioneered this technique. Initially, no great concern was attached to the surgical removal of clitoris because it was considered to be a vestigial organ. Surgeons originally believed that clitoridectomy was unlikely to seriously hamper the sexual functions of females. This was supported by three corroborative views. Firstly, Sigmund Freud classified female orgasm into vaginal and clitoral. He considered vaginal orgasm as the authentic and matured orgasm while clitoral orgasm as infantile. He even suggested that ablation of clitoral orgasm is a precondition for the proper development of female sexuality. Secondly, Earnest Grafenberg discovered a “G-spot” in the anterior vaginal wall which, according to him, was responsible for female orgasm (also known as G-spot orgasm or urethral orgasm). Discovery of G-spot reduced the physiological importance of clitoris. Lastly, John Money popularized the concept of “nature versus nurture” after studying the unfortunate case of one David Reimer. This infant boy lost his penis following a circumcision-accident. He was feminized by genitoplasty and his name was changed to Brenda. Money, on comparing Brenda and “his” identical twin brother, concluded that all infants are gender-neutral at birth; child rearing practices rather than the biological nature determine the gender identity. He advocated early sex assignment in genital ambiguity to avoid gender confusion at a later age. Based on these arguments, prior to 1980s, infantile clitoridectomy had become the norm in the management of CAH.

SURGERY OF CAH - CLITORAL PRESERVATION

By the turn of 1970s several strong voices began to criticize and condemn clitoridectomy. The most vociferous of them was from the women’s liberation groups. Feminists considered clitoridectomy as a form of genital mutilation and they equated it symbolically with suppression or denial of feminine rights. Acclaimed sexologists such as Alfred Kinsey, William Masters - Virginia Johnson and Shere Hite refuted Freud’s view of orgasm. They claimed that clitoral stimulation is the only way of achieving female orgasm and they denounced vaginal orgasm as a myth. They also denied the existence of G-spot. These modern sexologists attributed vaginal and G-spot orgasms to the inevitable overlap of concomitant clitoral stimulation during genital manipulations. Adding to these, Milton Diamond challenged Money’s “nature versus nurture” theory. Diamond followed-up Money’s patient - David Reimer - in his late teens and found that Reimer was completely dissatisfied with his assigned sex (female). Diamond established that only biological nature prevails irrespective of the sex of rearing. These groundbreaking evidences compelled surgeons to design new feminizing operations by preserving the clitoris. Clitoroplasty such as nervesparing clitoral reduction and clitoral recession gradually replaced clitoridectomy.

CLITORIDECTOMY VERSUS CLITOROPLASTY

Science was the casualty in the controversy of female orgasm. Switching from clitoridectomy to clitoroplasty was largely due to societal pressure rather than science. Cosmetically both the procedures gave comparable results (fig.3,4). But there were no hardcore evidences for the functional superiority of one procedure over the other. In 2003, Minto et al published the long-term sexual outcome of children who had undergone clitoral surgery for CAH and androgen insensitivity. They studied 27 children of whom 12 had clitoridectomy, 4 had clitoral reduction, one had clitoral recession and 10 had no clitoral surgery despite abnormal genitalia (controls). The study cohort was evaluated with Golombok-Rust Inventory of Sexual Satisfaction (GRISS). Orgasm was achieved in 60% of non-surgical cohort (controls) as compared to only 41% in those who had any one form of clitoral surgery. Among the surgical cohort, orgasm was achieved in 50% of those who had clitoridectomy as compared to only 20% of those who had the clitoris preserved. This is contrary to our expectations. Authors of the paper opined that any form of clitoral surgery, by causing damage to clitoral nerves, may result in orgasmic difficulties. I wish to interpret this seminal paper from different angle of view. To my mind this paper poses three puzzles:

Figure 3: Cosmetic outcome of clitoridectomy in a CAH toddler. A and B depict pre- and post-operative appearance respectively
3. What was the reason for orgasmic difficulty in 80% of those who underwent surgery for ambiguous genitalia? For this reason Sayin30 emphasized the concept of “Blended orgasm” wherein the deficiency of one sensory input is compensated by others to meet the required total input for achieving orgasm. It is now clear that a woman can experience orgasm despite clitoridectomy through alternate pathways. The new theories of female orgasm may shift the focus of genitoplasty from the compulsion of clitoral preservation to cosmetic excellence in CAH.

**Puzzle 3: Anorgasmia despite clitoral preservation**

Female anorgasmia in CAH despite clitoral preservation can be explained by the phenomenon of androgen imprinting. High androgen level during the critical period of sexual differentiation is known to masculinize the fetal brain not only in human beings but also in lower animals and primates. As the first peak of serum androgen occurs at 12 to 20 weeks of gestational life, androgen imprinting of brain occurs as early as second trimester of pregnancy. The androgen-imprinted brain exhibits male traits such as sexual attraction towards a female irrespective of the phenotype or genotype of the host individual. Thus, a female CAH person is likely to be attracted towards another female (homosexuality) because of the masculinized brain consequent to high levels of testosterone during fetal life. Evidences indicate that the degree of androgenization is related to the severity of CAH and thereby to prenatal androgen excess. For example, homosexuality is more common in classical salt-wasters (severe form of CAH) than in non-classical type (mild form of CAH). Thus, women with classical CAH are less likely to achieve orgasm through heterosexual (male partner) intercourse despite an optimal feminizing genitoplasty.

**A RATIONAL APPROACH TO SEX ASSIGNMENT IN CAH**

Previously all 46XX individuals with CAH were assigned female sex because of technical simplicity of feminizing genitoplasty. Such a simple solution is prone to be fallacious because CAH is a spectrum of disorder with varying degree of androgenization. It would be logical to assign male sex when the brain is severely masculinized in a 46XX - CAH. On the other hand, patients with minimal androgen imprinting can be raise as females. This rationalization will avoid the conflict between the assigned sex and subjective gender identity (sexuality).

Measuring the degree of brain androgenization is the new task. The surest way of doing this is to wait until the CAH patient reaches adolescence, when she can express her subjective inclination towards gender and sexuality. However, postponing sex assignment to adolescence has its own psychosocial perils such as confused gender development, school bullying, low self-esteem and poor body imaging. Such delaying may possibly even lead to “phantom genitalia” - a phenomenon analogous to phantom limb. On the other hand, it is impractical to ask a CAH infant about her gender and sexual orientation. Degree of brain androgenization cannot be predicted from the degree of genital virilization. Science is once again challenged with the problem of measuring the degree of brain androgenization and gender inclination of infants.

**ROLE OF PLAY TOYS IN SEX ASSIGNMENT**

Play toys appear to hold the clue for determining the projected sexual orientation of infants. It is universally observed that boys prefer ball, shape-sorting toys, magnets and toy cars while girls prefer Barbie dolls, jewelry, tea set, beads and vanity sets. In an extensive study, Blakemore and Centers have catalogued 126 toys as masculine, feminine and neutral toys. Although it was thought earlier that children develop gender-specific toy preference only at the age of 3...
years, recent evidences suggest that even infants as young as 1-year of age exhibit this phenomenon. Toy-preference is evolutionarily linked to biological preparedness towards gender-specific role play in later life. Skeptics raised concerns whether gender based toy-preference is a biological trait or is it a learnt social behavior. Toy-prediction can be used for sex assignment only if it is a biological trait. Independent studies in primates recently proved that gender specific toy-preference is an innate phenomenon. Even Vervet monkeys and rhesus monkeys exhibited sex-specific toy-preference paralleling human children.

Female CAH children with masculinized brain prefer masculine toys over feminine toys. This is attributed to prenatal exposure of fetal brain to high levels of androgen. The degree of prenatal androgenization of brain is proportionately related to strong desire for masculine toys. Thus, girls with severe form of CAH showed strong attraction towards male toys and those with milder disease frequently chose feminine toys as well. Importantly gender based toy-selection in CAH patients is not influenced by parenting and postnatal socialization.

Overwhelming scientific evidences suggest infantile toy-preference could be a reliable guide for sex assignment. Female CAH infants showing strong interest in masculine toys may be assigned male sex while those preferring feminine toys can be raised as girls. Further long-term clinical studies are required to standardize the procedure. Benefits of sex assignment based on toy-preference may even go beyond CAH. Currently, sex is assigned based on the appearance of external genitalia. It is acknowledged that brain is the most important sex organ. Therefore, sex assignment based on brain’s sexual orientation could be the most logical and natural way of doing it. This may even solve the dissonance between the body and the mind - not only in intersexuals but also in homosexuals and transsexuals.

**CONCLUSION**

Ladies and Gentlemen, when a woman is not a woman, it is not only a mystery but also a misery. Science is slowly unraveling the mystery to solve the misery. It may not be too far when CAH children will be sub-categorized and assigned with sex according to the degree of disease severity and degree of androgenization of brain. This will be facilitated by more understanding and standardization of gender specific toy-preferences.

**REFERENCES**

1. Biography of late Dr Pinnamaneni Narasimha Rao (Personal communication from IMSA world headquarters - 2012)
5. Benjamin H. Sex is what you see and gender is what you feel; Comfort with each is necessary for happiness. Presented at International Gender Symposium; Norfolk 1972
6. Raventhiran V. Long-term outcome of Disorders of Sexual Differentiation. Lecture delivered at Seminar on Disorders of Sexual Differentiation, Tamilnadu MGR Medical University, Chennai on 4th November 2011
A child may be born with genetic, gonadal and phenotypic sex with the 3 sexes in concordance with each other. This is considered ‘normal’ and is the largely prevalent mode of recognizing binary gender assignment. Gender assignment is, thus, the role which the individual is expected to engage in with suitable psychosexual orientation. However, when the 3 sexes are in discordance, the socio-cultural environment, customs and family sentiments significantly influence decision making. There lies the enigma of disorders of sex development (DSD).

Since the 1950s, DSD infants born with ambiguous genitalia have been surgically altered and assigned a gender that in part is based on sex role stereotypes. The presence of an “adequate” penis (one that is capable of vaginal penetration and will allow the male to stand while urinating) in an XY infant has led to the label “male.” The absence of an “adequate” penis has led to the assignment of the child to the female sex and surgical alteration of the infant’s genitalia into a more acceptable female appearance, even if it renders the XY child infertile as an adult.

XX infants have not been similarly treated. An XX infant, who is capable of reproducing, typically has been assigned the female sex to preserve her reproductive capability, regardless of the appearance of her external genitalia. If her “phallus” is considered too large to meet the guidelines for a typical clitoris, it has been surgically reduced, even if the reduction reduces or destroys her capacity for satisfactory sexual intercourse. In other words, males have been defined by their ability to penetrate and females have been defined by their ability to procreate. Infants with atypical chromosomal patterns (neither XX nor XY) and ambiguous genitalia typically have been turned into females.

In 2006, a survey was conducted among Pediatric Urologists. The respondents overwhelmingly favored female gender assignment for females with congenital adrenal hyperplasia (CAH) even if they were extensively masculinized (Prader type V). They recommended feminizing surgery - reducing the size of an enlarged clitoris - and if that was not enough, they recommended preservation of female fertility was of foremost importance and the masculinization of behaviors or inclinations, was of lesser importance. There was a great difference of opinion as to the age it would be best to do the surgery.

On the other hand, there has been a paradigm shift in the management of aphallia (congenital absence of penis). In the past, gender reassignment was the preferred approach. However, prenatal and postnatal effects of androgens on brain, were recognized as causing a male-typical shift in terms of psychosocial and psychosexual development, resulting in gender dysphoria later in life. As a result, the current trend is to rear these children as males.

The orator has given his insights into different prevalent philosophies on clitoral surgery. He has dissected the issue considering varied clinical scenarios, such as, 1: Orgasmic difficulty despite no surgery, 2: Orgasm despite clitoral excision, citing examples of studies which include brain mapping after genital stimulation, 3: Anorgasmia despite clitoral preservation and 4: Role of play toys in sex assignment.

It is hoped, that, a pragmatic approach and consensus could be build especially, while addressing such problems in the developing countries where children are often brought late and already given a gender assignment, particularly when it is male. Age at consent, fertility issues, development of malignancies in retained gonads and gender dysphoria later in life should be taken into consideration while taking crucial decisions in DSD.

REFERENCES


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