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THE DIAGNOSIS AND TREATMENT OF AMBISEXUALISM IN CHILDREN

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THE concept of what constitutes the sex of an individual has changed considerably in recent years. In most cases, the sex of a newborn infant is decided in the delivery room, and it is usually an obvious decision based on the type of external genitalia. In some instances, abnormal development of the external genitalia makes it difficult to determine the sex, and it is these cases of ambisexualism that are discussed in this paper.

Sex-Determining Factors

The primary factors that determine the sex of an individual are: (1) the chromosomal pattern of the individual cells; (2) the type of gonad; (3) the hormonal pattern and its effect on various tissues and organs; (4) the external genitalia, internal genital ducts, and secondary sexual characteristics; (5) the psychic reactions that are influenced by the environmental experiences of the individual. Since each person is a combination of the male and the female elements, it appears that the sex of any one person is the algebraic sum of all the factors mentioned above and not just any one of them.[1,2]

Types of Ambisexualism

Because of the problems in the clinical determination of sex, it is important to develop a working classification of ambisexualism. In general, patients whose sex is in question may be classified according to four large clinical groups: (1)

adrenogenital syndrome, (2) gonadal dysgenesis, (3) pseudohermaphroditism, and (4) true hermaphroditism.

Adrenogenital syndrome. Hyperadrenocorticism will produce any one of a variety of syndromes, but the discussion in this report will be confined to the adrenogenital syndrome in the female with virilization, since this is the syndrome that produces a problem of the differentiation of sex in the young child. In childhood the adrenogenital syndrome is the most common adrenal disorder, and more often affects females than it does males.

The adrenogenital syndrome may be due either to bilateral adrenal hyperplasia or to an adrenocortical tumor, but in the congenital form it is usually secondary to adrenal hyperplasia. There is considerable evidence that suggests the existence of a partial defect in the synthesis of hydrocortisone with an inability of the adrenal gland to convert 17-hydroxyprogesterone to hydrocortisone.[3-5] The lack of normal amounts of hydrocortisone stimulates increased release of corticotropin (ACTH) by the anterior pituitary, which would concomitantly cause an increase in production of androgen by the adrenal gland. These increased concentrations of androgen produce the virilization seen in the adrenogenital syndrome.

The increase in protein anabolism from the increased amounts of circulating androgen initially greatly accelerates growth, though the epiphyses close prematurely and the over-all effect is one of diminished stature. The excessive amounts of androgen interfere with the development of the external genitalia, and may result in hypertrophy of the clitoris, fusion of the labial folds, and diminution in the size of the vagina. Secondary sexual characteristics develop early with definite evidence of masculinization.[6]

Patients having adrenogenital dysfunction sometimes show additional signs associated with the adrenogenital syndrome. Approximately 30 per cent of these patients may present with an addisonian-like picture, and represent problems in electrolyte balance.[7] Another group of patients often have associated hypertension, and a third group has disturbances of carbohydrate metabolism.

Gonadal dysgenesis. Patients with gonadal dysgenesis may have either male or female sex chromosomes. Gonadal aplasia was described in 1938 by Turner,[8] who reported a group of girls with infantilism, cubitus valgus, and webbed neck. These were initially believed to be cases of ovarian agenesis, but later studies of sex chromosomes showed that the majority of these patients have the male configuration. These patients represent failure of gonadal development and genetically may be either male or female. Characteristically they are of small stature, have female external and internal genitalia, and sexual infantilism.[9]

The experimental work of Jost[10] revealed the mechanism involved in ambisexualism, particularly in those persons who have a male genotype and a female phenotype. He found that castration of fetal rabbits at an early stage in development, and replacement of the embryos into the amniotic cavity, resulted in female differentiation of the internal genital ducts and external genitalia. On the other

hand, removal of the ovary in no way affected the developing embryo. It thus appears that the morphogenetic substance of the fetal testes is necessary for differentiation of the male genital ducts and external genitalia. In gonadal aplasia the absence of secretions from the gonad permits female differentiation to occur whether the genetic sex is male or female.

Gonadal dysplasia (Klinefelter's syndrome) is characterized by male habitus, small testes, azoospermia, and gynecomastia. Persons with gonadal dysplasia often seek medical advice after puberty because of an infertility problem or the gynecomastia. Testicular biopsies show nearly complete fibrosis of the seminiferous tubules, but intact Leydig cells. The urine contains high concentrations of the follicle-stimulating hormone (FSH). The sex chromosomes were female in the majority of such persons, according to buccal smears.[11]

Del Castillo, Trabucco, and De la Balze[12] described a small group of patients having features similar to those seen in Klinefelter's syndrome, but without high concentrations of FSH in the urine. Testicular biopsies showed no germ cells, but intact Sertoli cells, and the majority of these patients had male sex chromosomes.

The factor producing a male gonad in a person of the female genotype may be an aberration in the chromosomes. It is postulated that the formation of an XXY or an XYY arrangement may be the cause.[13] Others believe that there may be inhibitory or damaging substances that suppress the cortical development of the gonad.

Pseudohermaphrodites. Persons whose genotypes and gonads are similar, but whose external genitalia suggest the opposite sex, are classed as pseudohermaphrodites. Male pseudohermaphrodites have male sex chromosomes and testicular gonadal tissue, but the external genitalia are ambiguous or female in type. This abnormality is best explained by assuming that the masculinizing hormones are abnormal or the tissues fail to respond to them. These patients may be divided into two groups: (1) those persons with ambiguous external genitalia, and in whom at puberty develop either male or female secondary sexual characteristics; and (2) those persons with female external genitalia. Persons in group 2 are often mistaken for normal females.[1]

Female pseudohermaphrodites without adrenal hyperplasia have female sex chromosomes and ovaries, but have masculinization of the external genitalia. This is a rare abnormality and is due to androgenic stimulation before complete development of the external genitalia. This has been reported[1] as having occurred in progeny of mothers with arrhenoblastomas or those receiving unusually large doses of progesterone during pregnancy.

True hermaphrodites. Persons who have both testicular and ovarian tissue are true hermaphrodites. The genotype may be either male or female, but the development of the external genitalia shows a great variety of gradations. About 70 cases of true hermaphroditism have been reported[14] to date.

Diagnosis of Ambisexualism

It is of paramount importance to investigate the patient with ambisexualism as early in his life as possible. The following abnormalities are indications for extensive study[2]: (1) deformity of the external genitalia; (2) hypospadias; (3) bilateral undescended testicles; (4) female external genitalia associated with palpable masses in the groin or labia majora.

Initally, sex-chromosome studies should be done on all patients in these groups. Among the first investigators in this field was Severinghaus,[15] who, using a complex procedure, identified the chromosomal sex in the nuclei of certain human cells. Barr, Bertram, and Lindsay[16] developed a more simplified technic that is practical and widely used today. By use of a special preparation, a mass of chromatin about one micron in diameter can be observed to lie against the inner surface of the nuclear membrane in from 50 to 90 per cent of cells examined in females, and from 0 to 20 per cent of cells in males. These chromatin masses can be identified in nearly all somatic cells, but epithelial cells obtained from buccal mucosal scrapings offer a reliable and satisfactory preparation. Whether this chromatin mass represents the adherence of 2X chromosomes or is something else is still a matter of great discussion.

After sex-chromosome studies are obtained, the group of patients with female pseudohermaphroditism secondary to adrenal hyperplasia must be differentiated from patients with other forms of ambisexualism. This can easily be done by obtaining a specimen of urine and determining the 17-ketosteroid excretion in a definite period, and also determining the concentration of pregnanediol.[6]

After the patients with adrenal hyperplasia have been identified, the determination of sex of the other patients becomes more complicated. Extensive studies of the anatomy must be made. A careful cystoscopic examination, looking for the presence of a vagina and cervix or a prostate, is a valuable diagnostic aid. Roentgen examinations, including the use of radiopaque material, as well as measurement of the urinary excretion of FSH and estrogens, are helpful in selected cases. After these preliminary studies have been carried out, it may be necessary to perform an exploratory operation and perform a biopsy on the gonads. When all the diagnostic findings are accumulated and evaluated, the sex-of-rearing can be determined and appropriate therapy instituted.

The selection of the sex-of-rearing should be based on the anatomic configuration of the external genitalia, particularly the size of the phallus or vagina and not primarily on the chromosomal or gonadal sex or structure of the internal genital ducts.[1] A female pseudohermaphrodite without adrenal hyperplasia is an exception to the above rule, provided a diagnosis is made in early infancy.

Extensive studies by psychiatrists interested in the problem of ambisexualism indicate that the sex toward which a child's upbringing is directed is the most important factor in the psychosexual orientation of the individual.[17,18] There is no evidence to indicate that bisexual or homosexual behavior develops more fre-

quently in ambisexual persons than in the general normal population.

Unfortunately when the sex of the external genitalia is doubtful, the decision as to the sex-of-rearing is sometimes delayed, producing confusion for both the child and his family. Psychologic studies indicate that alterations in the sex-of-rearing after two years of age frequently leave the patient in an unfortunate psychiatric state. When there is doubt regarding an infant's sex, this should be discussed immediately with the parents to prevent a public announcement of the sex of the child before it is confirmed. After the sex-of-rearing is decided on, it is again important to impress upon the parents that the child is a boy or a girl whose sexual organs were not completely differentiated at birth. This discussion must be carried on at the level determined by the intelligence of the parents. They must be told that it is most unlikely that their child will grow up with perverse sexual desires, for, in the layman's mind, ambisexualism is often confused with homosexualism.

Treatment of Ambisexualism

Female pseudohermaphroditism with congenital adrenal hyperplasia. In this syndrome the plan of therapy is to give fairly large doses of cortisone initially to obtain maximal adrenal suppression, and then to determine the minimal daily dose required for maintenance.[19] The initial dose is usually given intramuscularly for from 5 to 10 days, and then the appropriate maintenance dosage must be determined by following the patient with periodic 17-ketosteroid determinations and observations on bone growth and general development. Approximately one third of the patients with adrenogenital syndrome will have the electrolytic disorders seen in adrenal insufficiency. These patients must be hydrated with electrolyte solutions and treated with the appropriate steroids. Excessive steroids will produce a Cushingoid picture and a plateau in growth rate, so that the dosage used for maintenance must be constantly regulated.[20] These patients usually will recover from this salt-losing state and, as they grow older, supplemental steroids may not be required.

When the patient is two or three years of age, clitorectomy and separation of the fused labia majora should be performed.[21] When appropriate therapy is started early, growth and development occur at a normal rate. Those patients who have female pseudohermaphroditism secondary to adrenal hyperplasia but have been reared as males, should not be considered as being female. Plastic procedures can correct the hypospadias, and cortisone therapy given during childhood will prevent early epiphyseal ossification. Oophorectomy and hysterectomy will prevent feminization.

Gonadal aplasia. Persons with gonadal aplasia have infantile female internal and external genitalia. Fortunately, these persons are usually brought up as girls, although they may have male sex chromosomes.[22] Stunted growth, though frequently associated with this syndrome, is similar to that seen with primordial dwarfism for which there is no effective therapy. Plastic surgical procedures may

be necessary to correct some of the associated defects, such as the webbed neck seen in Turner's syndrome. When the patient is between 12 and 14 years of age, stilbestrol therapy is started, to permit normal endometrial development, breakdown, and menstruation. This therapy also produces rapid development of the breasts, labia, vagina, and uterus.[1]

Klinefelter's syndrome (gonadal dysplasia). In this syndrome, the testes are incapable of responding to gonadotropin. Often, sufficient androgens are produced to cause normal development of secondary sexual characteristics, but occasionally supplementary androgen therapy may be required. When present, gynecomastia does not respond to hormonal therapy; if it becomes a problem in management, mastoplasty may be performed.[23]

Male pseudohermaphroditism with external genitalia that resemble the female organs. Children with this abnormality usually develop feminine secondary sexual characteristics at puberty, but menstruation does not occur. These children should be reared as females, and orchiectomy should be performed, both to prevent any chance of masculinization and the development of malignant testicular tumors. After orchiectomy, supplemental estrogens may be given to allow normal female characteristics to develop, since the testes supply an important source of estrogen for these persons.[1]

Male pseudohermaphroditism with ambiguous genitalia. Children with this abnormality should be raised according to the functional ability of the external genitalia. If it is planned to raise the child as a female because of an exceedingly small phallus, orchiectomy should be performed fairly early to prevent possible masculinization. Plastic operative procedures should then be performed to make the genitalia conform as closely as possible to those of the female sex.

Female pseudohermaphroditism without adrenal hyperplasia. In children with this abnormality, normal female secondary sexual characteristics develop at puberty. It is important to recognize this syndrome early since these persons frequently may be raised as males. Clitorectomy and separation of fused labial folds are the only plastic procedures usually required.

True hermaphroditism. These hermaphrodites usually require the removal of the gonad that does not correspond to the sex-of-rearing. The remaining gonad will then usually direct secondary sexual development along the proper lines. In instances where ovotestes exist bilaterally, a part of each gonad may be removed. Often, plastic procedures are necessary to make the external genitalia conform as closely as possible to the sex-of-rearing.

Conclusions

Though hormonal treatment and the judicious use of surgical procedures are most important, the curative management of children with ambisexualism requires knowledge of the various entities that may produce this state, a great deal of

judgment in choosing the sex-of-rearing, and extraordinary understanding in treating both the child and his parents.

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