CAH: defeating and dogm

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By Dr Aysha Habib Khan

THE BIRTH of a child with ambiguous genitalia is a social emergency. The emotional one established by health care professional in conveying this message can have a lasting influence on how the parents conceptualize the abnormal genital development.

Therefore, a positive atmosphere is essential for parents to begin their relationship with their child. The decision as to the appropriate sex of the rearing of a baby born with ambiguous genitalia is based on a number of considerations that have an impact on the infant's future.

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is the most common cause of ambiguous genitalia in the newborn female. As affected females have the capacity for an entire female sex role including child bearing, it is important to recognize this disorder in the newborn with ambiguous genitalia, so that the girls are raised as females, an appropriate treatment plan is developed, prognostic information shared and accurate risk counselling communicated. In most other intersex conditions the potential for fertility is either reduced or absent.

CAH is an inherited disorder due to an enzyme deficiency in the adrenal glands, located on top of the kidneys, in the back near the waistline. The defect leads to an inability to make hormones (cortisol and/or aldosterone), necessary to maintain life. Cortisol is responsible for maintaining body's energy supply, blood glucose, and control of body's reaction to stress. Aldosterone is the salt-retaining hormone, necessary for maintaining a normal balance of salt and water in the body.

Instead of making cortisol, the hormonal raw materials are shifted to make other hormones, specifically male sex hormones (androgens). As a result more androgens are produced than required. The excess of androgens stimulates the growth of genitalia before birth. It does not create any problem when the child is male. However, excess androgen in a female with this disorder causes the child's genitalia to have the appearance of a male although the internal genitalia are normal female. This is called masculinization of the female genitalia.

Three main forms of CAH exist: salt wasting (SW) and simple virilizing (SV) form presenting within the first few days of life, and a milder form of nonclassical CAH, which presents in adult.

Analysis of CAH incidence data from almost 6.5 millions newborns screened in the general population worldwide has demonstrated an overall incidence of between 1 in 10,000 and 1 in 15,000 live births for the classic form of CAH. The disease frequency of nonclassic CAH (adult form) in the general population of New York City is 1 in 100, and 1 in 7 is a carrier.

An infant with the SW form may have vomiting, poor weight, poor feeding, drowsiness, diarrhoea and dehydration. Blood tests would reveal a lower than normal level of salt in the blood. The infant may go into shock and without proper treatment this infant may die. Male newborns with the SW form of CAH will have no outward physical sign except possible increased pigmentation around the genitalia. So their diagnosis can be easily missed. Female newborns with the SW form of CAH have ambiguous genitalia, which may make the infant appear partially or very much like a male. The clitoris of a female newborn with the SW form is enlarged and the labial folds may be somewhat joined and wrinkled to look like a scrotum. It does not generally cause illness in the newborns.

The external genitalia of females with the SV form of CAH are also ambiguous, having an enlarged clitoris with or without joining the labial folds. The degree to which the clitoris is enlarged and the labia are grown together will reflect how much the infant appears male. Other symptoms of the SV form of CAH develop with age in both males and females, including rapid growth in early childhood and seemingly early sexual development with pubic hair growth.

A milder form of CAH may appear anytime between early childhood and puberty. In early childhood, the mild form causes rapid growth and early pubic growth, acne, menstrual irregularity, and sometimes infertility. Infertility may also occur in males with this milder form of CAH, although it is not common.

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Production of enzymes is controlled by genes, which are areas on chromosomes with specific function. The chromosomal composition of an individual in turn comes from the parents, each contributing one half. This genetic makeup determines the child's features before birth. The gene for 21-hydroxylase can also be evaluated by DNA analysis, which determines whether the gene is present or absent, or if the DNA makeup is changed in the patient. CAH results when a child inherits two defective genes for adrenal enzymes production, one from each parent.

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The parents usually do not have this disorder because they are only carriers of this disorder, that is they have inherited one normal gene and one affected gene for the enzyme from their parents. The normal gene is dominant and blocks the expression of the defective gene.

When one carrier marries another carrier, there is a 25 per cent chance their child will inherit both the defec-

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ive genes and therefore have the disorder. There is an equal chance that their child will inherit both normal genes and not have this disorder, and there is a 50 per cent chance the child will inherit one normal and one defective gene and will therefore be a carrier of genetic trait.

A retrospective analysis in our group of patients of CAH has shown that consanguinity in the parents is present in 52.4 per cent of the cases, though none of the parents suffered from the disease. Also 30.2 per cent of the cases had similar features in the siblings. The other findings noted were history of death in neonatal period and infancy in the family and history of still births and abortions in mother. In another preliminary study on genetic analysis of CAH patients, we demonstrated a change in the DNA, which is also reported for other populations as the most commonly identified mutation. All our cases were appropriately assigned to paternal or maternal chromosomes.

When there is a family history of CAH, it is possible to diagnose a child before birth through tests performed during pregnancy. Regardless of whether the newborn is male or female, early diagnosis and medical treatment of CAH is crucial. Without treatment a newborn with the SW form of CAH is in a life threatening position. Generally, in the SV form of CAH, only cortisol replacement is necessary. In the SW form, replacement of both cortisol and the salt retaining hormone and extra salt are necessary. Since the body cannot produce enough cortisol in the SW form, synthetic cortisol (hydrocortisone) and synthetic salt retaining hormone (florinef) are given to supplement those that the body cannot produce.

The aim of treatment is to provide the body with the ability to maintain a normal energy level, and balance of salt and water in the body, normal growth and sexual maturation at puberty, and fertility in later life. Therefore, treatment of CAH is ongoing, involving periodic evaluations and monitoring for possible dose adjustment.

The masculinization of female's genitalia will require corrective surgery as an infant and possibly again later in life. However, treatment started early in the pregnancy may also reduce the degree of masculinization and may also reduce the risk or need for surgery later.

Children with CAH are being brought to medical attention much too late even now. In one of our studies, only 35 cases out of 62 were diagnosed in the newborn period. Wrong gender assignment to genotypic females were noted and in some of them male sex was maintained due to late presentation and development of male gender identity at diagnosis. A lot of this is due to lack of awareness, lack of proper diagnosis, false social beliefs, religious dogmas, pressure from relatives and society, etc. The primary need is to develop expertise for early case detection. A rational and judicious choice of sex assignment is a critical aspect of treatment, since the decision of sex assignment has obvious life long implications.

The issue of gender ambiguity has never been seriously addressed in Pakistan. Determinations of genetic sex by chromosomal analysis and accurate diagnosis are essential using a patient's potential for future sexual activity. Because of the high rate of consanguinity in our population it is important to establish the true incidence of the defect in our population.■