Three out of four: a case discussion on ambiguous genitalia

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Abstract

Disorders of sex development (DSD) include a heterogeneous group of heritable disorders of sex determination and differentiation. This includes chromosomal as well as monogenic disorders, which inhibit or change primarily genetic or endocrine pathways of normal sex development. However, in many patients affected, no definitive cause for the disorder can be found. Therefore, the birth of a child with ambiguous genitalia still represents an enormous challenge. For the structuring of diagnostic procedures, decision making and also therapeutic interventions, a highly specialised team of physicians of different subspecialties and experts for psychosocial care is needed to counsel parents and patients accordingly. This article presents a case with 46,XX DSD and androgen excess. After making the diagnosis on clinical and biochemical grounds, the family refused further genetic testing. The outcome of subsequent pregnancies confirmed the working diagnosis of an autosomal form of 46,XX DSD. However, the family still refused prenatal testing and treatment on religious grounds. The case discussion further illuminates the possible influence of religion in prenatal testing and concludes with the approach to the parents for comprehensive counselling in decision making for their child.

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Introduction

Disorders of sex development (DSD) include a heterogeneous group of heritable disorders of sex determination and differentiation. This includes chromosomal as well as monogenic disorders, which inhibit or change primarily genetic or endocrine pathways of normal sex development. However, in many patients affected, no definitive cause for the disorder can be found. Therefore, the birth of a child with ambiguous genitalia still represents an enormous challenge. For the structuring of diagnostic procedures, decision making and also therapeutic interventions, a highly specialised team of physicians of different subspecialties and experts for psychosocial care is needed to counsel parents and patients accordingly. This article focuses on the genetic and molecular origins of DSD, the new DSD nomenclature, the consecutive classification, and steps for diagnosis. Furthermore, we discuss the approach to the family for comprehensive counselling in decision making for their child.

Case report

A child was presented to the Paediatric Endocrine Department because sex determination could not be performed. The parents of the child were non-consanguineous Turkish immigrants. The child was a product from the mother’s first pregnancy which was uncomplicated. There was no known drug or medication use and the mother had no signs of androgen excess such as hirsutism, acne, alopecia or clitoral hypertrophy. There was no family history of infertility, ambiguous genitalia or unexplained neonatal deaths.

Physical examination showed a Caucasian child with pinkish-brown skin colour who was normally proportioned and had no dysmorphic features. Stretched phallic length was not measured initially and the urethral opening could not be localised. A blood sample was collected for karyotype and measurement of the main adrenal steroid precursors. Blood glucose and serum electrolyte concentrations were normal. Ultrasound examination showed the presence of uterus and ovaries.

The karyotype in combination with an increased 17-hydroxyprogesteron (17OHP) confirmed the likely diagnosis of a 46,XX DSD with androgen excess caused by congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. The parents were informed of the diagnosis and rearing of a female sex was agreed. Treatment with hydrocortisone was started. Daily
measurements of weight and serum glucose, sodium and potassium were performed. A diagnosis of classical salt losing CAH was confirmed with 129 mmol/l serum sodium. Fludrocortisone and sodium chloride supplements were added to the treatment regimen. The family received support from the local multidisciplinary team (MDT) with experience in DSD (1). Genetic testing was suggested to absolutely confirm the diagnosis, but this offer was rejected by the parents. The infant was subsequently discharged from hospital. Thereafter, there was a period characterised by poor compliance with treatment, which resulted in increased levels of 17OHP. Members of the MDT were unable to make contact with the parents, other than the surgeon who was urged by the parents to proceed with genital reconstruction.

A vaginoplasty and clitoral reduction was performed at 1 month of age. The family was then lost to follow-up until the mother re-presented in her second pregnancy at 14-weeks gestation. Dexamethasone treatment was started immediately, but was stopped at 20-weeks gestation because a prenatal ultrasound performed at another hospital showed a male foetus. It was recommended that dexamethasone treatment be continued until chorionic villus sampling could confirm the male karyotype. However, this advice was not accepted and a healthy male infant was delivered at term.

During the third pregnancy, the parents did not opt for dexamethasone treatment because of potential side effects, and genetic testing was also declined for religious reasons. The infant was delivered at home, but the midwife admitted the child to hospital because of ambiguous genitalia. Subsequent tests confirmed 46,XX DSD due to CAH in a severely virilised child (Prader stage IV). Despite having two girls with CAH, the parents did not choose dexamethasone at the next pregnancy. Home delivery was again chosen and this time genetic testing was undertaken on cord blood. A male infant was born with CAH, as confirmed by a classic mutation in the CYP21A2 gene.

**Discussion**

How broad should the differential diagnosis be when the index case presented with indeterminate sex assignment? Based on the revised nomenclature, the ambiguous genitalia could either have been the result of androgen excess in 46,XX DSD or a disorder in androgen synthesis or action in 46,XY DSD. Ovotesticular DSD, although rare, was also a possibility. However, because of a high a priori chance of CAH, 46,XX with androgen excess was chosen as the working diagnosis. Initial tests were limited to a karyotype, adrenal steroid precursors (17OHP, androstenedione and DHEA sulphate) and testosterone. For completeness, the following categories of causes could be included in the differential diagnosis: ovotesticular DSD, partial gonadal dysgenesis, maternal or fetoplacentandrogen excess.

It is necessary to measure glucose and electrolytes from the first day of life when salt losing CAH is expected. Classical hypogonadism, hyperkalaemia seldom occurs early, but the rare form of CAH, congenital lipoid adrenal hyperplasia, presents with early metabolic disturbance. It is also important to follow an initial FISH analysis of the sex chromosomes with a full karyotype as the initial result may be based on a 46XX/46XY mosaic.

No tests of gonadal function were performed because of two reasons. Firstly, the physiological decrease in gonadotrophin-releasing factor stimulation after birth renders the infant in a physiological hypogonadotrophic state with low basal levels of luteinizing hormone and follicle-stimulating hormone. Secondly, it was decided to follow the working diagnosis of CAH, and only if this diagnosis was excluded would the investigation of gonadal function be performed.

Measurement of adrenal steroid precursors during the early postnatal phase is often invalid due to the potential interference in the assays from closely related steroids. It has been suggested that the tests are repeated 2–3 days after birth (1). Some centres may perform an adrenocorticotrophic hormone stimulation test shortly after birth. While this test can exclude hypogonadism, interference in the 17OHP assay may still render a definitive diagnosis of CAH based on biochemical tests not possible so soon after birth. Chromatographic analysis of the samples would be required. The high likelihood of CAH influenced the diagnostic work in the present case. Imaging the internal genitalia was given high priority but one must be certain of having confidence in the reliability of the technique. It is doubtful whether ovaries were readily identified since these are often not seen on ultrasound during this phase of low gonadotrophin stimulation.

The initial result of the karyotype combined with high levels of 17OHP was sufficient to inform the parents about the probable diagnosis of CAH. Treatment was started with hydrocortisone, while fludrocortisone treatment and additional sodium supplementation was delayed with the onset of electrolyte disturbance. Metabolic disturbance, including hypoglycaemia, can occur very early and may not always be delayed until the second week of life. The degree of virilisation is not necessarily correlated with the level of androgens in the affected female infant.

The MDT involved in DSD management should be introduced to the family at an early stage. The final diagnosis and sex determination is the responsibility of the MDT in conjunction with the family. In this particular case, perhaps a religious scholar should also have participated in the counselling in view of the specific religious and cultural beliefs. Initially, the parents appeared to be preoccupied with how to explain the DSD problem to their relatives and family, than what
the future held for their child. In certain cultural settings, the religious scholar is invited to join the MDT in discussions with the family. In the present case, the parents were strongly of the opinion that their daughter should have surgery as early as possible. There has been much debate on the timing and extent of surgery in CAH (1–3). The age between 2 and 6 months coincides with a period when the tissues in the vaginal wall are oestrogen stimulated from the transient rise in gonadotrophins, which improves wound healing. It is generally accepted that performing surgery at 1 month of age is too early. The emphasis of surgery is now focussed more on outcome of sexual function in adulthood, recognising that the clitoris is highly innervated and can be damaged during clitoroplasty (4). Clitoral reduction surgery is no longer undertaken for mild clitoromegaly (Prader stages I and II), but there remains no consensus on the timing for any surgery and whether vaginoplasty should be performed early or late.

Subsequent pregnancies were characterised by communication problems and poor treatment compliance. Consequently, prenatal treatment with dexamethasone was not started until 14 weeks of gestation. By this stage, it is assumed that the female external genitalia are already significantly virilised. However, phallic enlargement mostly occurs from fetal androgen stimulation in later pregnancy, so introducing dexamethasone in high-risk pregnancies during the second trimester may still be worthwhile to prevent further virilisation. It is unfortunate that the decision not to treat was taken without prior discussion with the MDT. Islamic law, or Sharia allows sufficient latitude to perform prenatal testing or even termination of pregnancy if the mother’s health is in danger or the outcome of the pregnancy is likely to be fatal. In several Islamic countries the use of genetic testing is actually encouraged, ensuring that an appropriate balance is struck between potential benefits and harm (5).

In conclusion, the literature on CAH is dominated by explanations of pathophysiology, diagnostic tests and treatment of the different forms of the adrenal disorder. However, communicating the diagnosis and supporting the family in coping with the consequences is equally as important. Members of the MDT need to guide the parents through discussions surrounding decisions about reconstructive surgery, genetic counselling and the importance of treatment compliance. Families from ethnic minorities may also benefit from early consultation with and support from their cognate religious scholars.

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