

AMBIGUOUS GENITALIA

Introduction

Ambiguous genitalia (AG) of the newborn is the paradigm of a disorder of sex development. This includes infants with bilateral cryptorchidism, perineal hypospadias with bifid scrotum, clitoromegaly, posterior labial fusion, phenotypic female appearance with palpable gonad (with or without inguinal hernia), and infants with discordant genitalia and sex chromosomes.

The word intersex has been in use for some time, but is not favored by many families with AG. The Chicago Consensus in 2006 recommended nomenclature to replace intersex with the umbrella terminology 'disorders of sex development' (DSD). This is defined as a congenital condition in which development of chromosomal, gonadal, or anatomical sex is atypical. Below is a summary of the components of the revised nomenclature

Table 1. Nomenclature relating to disorders of sex development (DSDs)

| Previous | Proposed |
|---|------------------------------------|
| Intersex | DSD |
| Male pseudohermaphrodite, undervirilization of an XY male, and undermasculinization of an XY male | 46, XY DSD |
| Female pseudohermaphrodite, overvirilization of an XX female, and masculinization of an XX female | 46, XX DSD |
| True hermaphrodite | Ovotesticular DSD |
| XX male or XX sex reversal | 46, XX testicular DSD |
| XY sex reversal | 46, XY complete gonadal dysgenesis |

Ambiguous Genitalia is a neonatal emergency

The commonest cause of AG is congenital adrenal hyperplasia (CAH).

Major concerns are :-

- underlying medical issues
 - dehydration, salt loss (adrenal crisis)
 - urinary tract infection
 - bowel obstruction
- decision on sex of rearing
 - avoid wrong sex assignment
 - prevent gender confusion
- psychosocial issues

General concepts of care

- *gender assignment* must be avoided before expert evaluation in newborns.
- evaluation and long-term management must be performed at a center with an experienced multidisciplinary team (Paediatric Subspecialists in endocrinology, surgery, and/or urology, psychology/ psychiatry, gynaecology, genetics, neonatology, and if available, social work, nursing and medical ethics.)
- all individuals should receive a gender assignment
- open communication with patients and family is essential, and participation in decision making is encouraged
- Patients and family concerns (eg, social and culture) should be respected and

EVALUATION

Ideally, baby/child with parents should be brought to a competent multidisciplinary team.

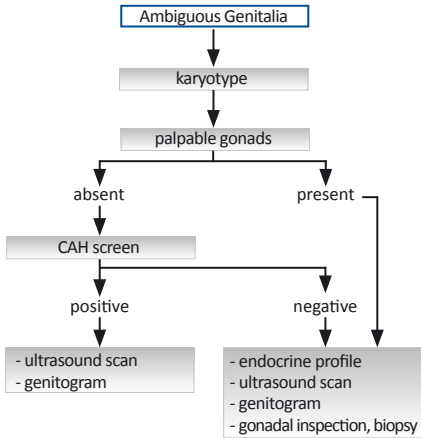
HISTORY - exclude CAH in all neonates

- parental consanguinity.
- obstetric : previous abortions, stillbirths, neonatal deaths.
- antenatal : drugs taken, exogenous androgens, endocrine disturbances.
- family History: Unexplained neonatal deaths in siblings and close relatives
 - infertility, genital anomalies in the family
 - abnormal pubertal development
 - infertile aunts
- symptoms of salt wasting in the first few days to weeks of life.
- increasing pigmentation
- progressive virilisation

Physical examination

- dysmorphism (Turner phenotype, congenital abnormalities)
- cloacal anomaly
- signs of systemic illness
- hyperpigmentation
- blood pressure
- psychosocial behaviour (older children)
- appearance of external genitalia
 - size of phallus, erectile tissue
 - position of urethral opening (degree of virilisation)
 - labial fusion / appearance of scrotum
 - presence / absence of palpable gonads
 - presence / absence of cervix (per rectal examination)
 - position & patency of anus

Figure 1. Approach to ambiguous genitalia



Investigations

- chromosome study, karyotyping with X- and Y-specific probe detection
- abdominopelvic ultrasound
- genitogram
- exclude salt losing CAH
- serial BUSE in the neonatal period
- serum 17-hydroxyprogesterone (taken after the first day of life)
- cortisol, testosterone, renin
- testosterone, LH, FSH
- anti mullerian hormone (depending on indication and availability)

Additional investigations as indicated:

- LHRH stimulation test
- hCG stimulation tests (testosterone, dihydrotestosterone (DHT) at Day 1 & 4)
- urinary steroid analysis
- androgen receptor study (may not be available)
- DNA analysis for SRY gene (sex-determining region on the Y chromosome)
- imaging studies
- biopsy of gonadal material in selected cases.
- currently, molecular diagnosis is limited by cost, accessibility and quality control.
- trial of testosterone enanthate 25 mg IM monthly 3x doses
 - this can be done to demonstrate adequate growth of the phallus and is essential before a final decision is made to raise an ambiguous child as a male.

Table 2. Differential diagnosis

| Uterus present | Uterus absent |
|---|---|
| 46,XX DSD virilising CAH foetal exposure to excessive androgens | 46, XY DSD androgen insensitivity syndrome 5-alpha reductase deficiency defect in testosterone synthesis |
| 46, XY DSD 46,XY gonadal dysgenesis | |
| Sex chromosome DSD 45, XO/46, XY gonadal dysgenesis | |
| Ovotesticular DSD true hermaphroditism | |

Table 3. Key features to aid diagnosis

| Hyperpigmentation | + | - | - | - |
|-------------------|---------------------------|-------------------------|---|----------------------------------|
| Palpable gonad(s) | - | + | + | + |
| Uterus present | + | + | - | - |
| Dysmorphism | - | + / - | - | - |
| Systemic illness | + | - | - | - |
| Diagnosis | 21-Hydroxylase deficiency | Gonadal dysgenesis | Partial androgen insensitivity syndrome | Testosterone biosynthesis defect |
| Karyotype | 46, XX | XO/XY 46, XY; 46, XX | 46, XY | 46, XY |

Management

Goals

- preserve fertility
- ensure normal sexual function
- phenotype and psychosocial outcome concordant with the assigned sex

General considerations

- admit to hospital. Salt losing CAH which is life threatening must be excluded.
- urgent diagnosis
- do not register the child until final decision is reached
- protect privacy of parents and child pending diagnosis
- counseling of parents that DSD conditions are biologically understandable.
- encourage bonding

Gender Assignment

Gender assignment and sex of rearing should be based upon the most probable adult gender identity and potential for adult function. Factors to be considered in this decision include :-

- diagnosis
- fertility potential
- adequacy of the external genitalia for normal sexual function. Adequate phallic size when considering male sex of rearing
- endocrine function of gonads. Capacity to respond to exogenous androgen.
- parents' socio-cultural background, expectations and acceptance
- psychosocial development in older children
- decision about sex of rearing should only be made by an informed family after careful evaluation, documentation, and consultation

Gender reinforcement

- appropriate name
- upbringing, dressing
- treatment and control of underlying disease e.g. CAH
- surgical correction of the external genitalia as soon as possible

Assigned female

- remove all testicular tissue
- vaginoplasty after puberty
- no place for vaginal dilatation in childhood

Assigned male

- orchidopexy
- remove all Mullerian structures
- surgical repair of hypospadias
- gonadectomy to be considered if dysgenetic gonads

Surgical management

- the goals of surgery are:
 - genital appearance compatible with gender
 - unobstructed urinary emptying without incontinence or infections
 - good adult sexual and reproductive function
- the surgeon has the responsibility to outline the surgical sequence and subsequent consequences from infancy to adulthood. Only surgeons with the expertise in the care of children and specific training in the surgery of DSD should perform these procedures
- early genitoplasty is feasible only if the precise cause of DSD has been established and gender assignment has been based on certain knowledge of post pubertal sexual outcome. Other wise surgery should be postponed, as genitoplasty involves irreversible procedures such as castration and phallic reduction in individuals raised females and resection of utero-vaginal tissue in those raised male.
- the procedure should be anatomically based to preserve erectile function and the innervations of the clitoris
- emphasis in functional outcome rather than a strictly cosmetic appearance.
- timing of surgery: it is felt that surgery that is performed for cosmetic reasons in the first year of life relieves parental distress and improves attachment between the child and the parents; the systematic evidence for this is lacking.

CONGENITAL ADRENAL HYPERPLASIA (CAH)

Neonatal diagnosis and treatment

- the newborn female with CAH and ambiguous external genitalia requires urgent expert medical attention
- the ambiguity is highly distressing to the family; therefore, immediate comprehensive evaluation is needed by referral to a pediatric endocrinologist
- ensure parents develop a positive relationship with their child

Clinical evaluation in term and premature neonates

- every newborn with ambiguous genitalia, a suspected diagnosis of CAH, or an abnormal result in a newborn screen for 17-hydroxyprogesterone (17OHP) should be evaluated by a pediatric endocrinologist
- the evaluation of an infant with ambiguous genitalia have been discussed above.

Newborn screening for CAH

- neonatal mass screening for 21-hydroxylase deficiency identifies both male and female affected infants, prevents incorrect sex assignment, and decreases mortality and morbidity. However, it has not been started in Malaysia yet.

Clinical presentation

Neonatal period

- ambiguous genitalia
- salt loss (75%)
- family history of previous unexplained neonatal death
- hyperpigmentation (90%) - both sexes
- boy with precocious puberty but small testis (volume <4 ml)
- virilisation of a girl
- hypertension

Diagnosis of salt-wasting CAH

- may not be apparent in the first days/weeks after birth by electrolyte measurements
- salt wasters may be differentiated from simple virilizers by :
 - serial serum/plasma and/or urine electrolytes
 - plasma renin activity (PRA) or direct renin
 - results of CYP21 molecular analysis

Management of salt losing crisis

- for patient in shock: normal saline (0.9%) bolus : 10-20 ml/kg
- correct hypoglycemia if present : 2-4 mg/kg of 10% glucose
- correct hyperkalaemia with administration of glucose and insulin if necessary.
- rehydrate using $\frac{1}{2}$ NS 5% dextrose
- monitor hydration status, BP, HR, glucose

Note: Hypotonic saline or 5% dextrose should not be used because it can worsen hyponatraemia

Treatment considerations in patients with CAH

Optimal glucocorticoid dosing

- aim to replace deficient steroids, minimize adrenal sex hormone and glucocorticoid excess: thus preventing virilization, optimizing growth, and protecting potential fertility
- during infancy, initial reduction of markedly elevated adrenal sex hormones may require hydrocortisone (HC) up to 25 mg/m²/d, but typical dosing is 10–15 mg/m²/d in 3 divided doses. Divided or crushed tablets of HC should be used in growing children
- excessive doses, especially in infancy, may cause persistent growth suppression, obesity, and other Cushingoid features. Therefore, avoid complete adrenal suppression.
- whereas HC is preferred in infancy and childhood, long-acting glucocorticoids may be used at or near the completion of linear growth. Prednisolone needs to be given twice daily. (at 2–4 mg/m²/d). Dexamethasone dose is 0.25–0.375 mg/m²/d, given once daily.
- in children with advanced bone age and central precocious puberty, treatment with a GnRH agonist may be required

Mineralocorticoid use

- all classic CAH patients should receive fludrocortisone at diagnosis in the newborn period
- dosage requirements in early infancy range from 0.05–0.30 mg/d, whereas typical maintenance doses are 0.05–0.2 mg/d, depending on the sodium intake

- therapy will reduce vasopressin, ACTH levels and lower dosage of glucocorticoid required
- the need for continuing mineralocorticoids should be assessed based on PRA and BP.
- sodium chloride supplements are often needed in infancy, at 1-3 g/day (17-51 mEq/day), distributed in several feedings.

Monitoring treatment for classic CAH

- monitoring may be accomplished based on physical and hormonal findings suggestive of excessive or inadequate steroid therapy
- laboratory measurements may include serum/plasma electrolytes, serum 17OHP, cortisol, and/or testosterone, and PRA or direct renin, every 3 months during infancy and every 4–12 months thereafter
- the time from the last glucocorticoid dose should be noted; the diurnal rhythm of the adrenal axis should be taken into account. Patients receiving adequate replacement therapy may have cortisol levels above the normal range.
- ideally, laboratory data will indicate a need for dose adjustments before physical changes, growth, and skeletal maturation indicates inadequate or excessive dosing.
- patients should carry medical identification and information concerning their medical condition and therapy

Treatment with glucocorticoids during stress

- parents must be given clear instruction on stress dosing
- because circulating levels of cortisol increase during stress, patients should be given increased doses of glucocorticoids during febrile illness ($>38.5^{\circ}\text{C}$), when vomiting or poor oral intake, after trauma and before surgery
- participation in endurance sports may also require additional steroid dosing
- mental and emotional stress, such as school examinations, does not require increased dosing
- stress dosing should be 2–3 times the maintenance glucocorticoid dose for patients able to take oral medications
- surgical and trauma patients and those unable to take oral steroids require parenteral hydrocortisone
 - below 3 years old: to give 25mg, followed by 25-30mg/day
 - 3-12 years old: to give 50mg, followed by 50-60 mg/day
 - >12 years old: to give 100mg, followed by 100mg/day
- glucose concentrations should be monitored, and intravenous sodium and glucose replacement may be required.

Genital surgery

- the decision for surgery and the timing should be made by the parents, together with the endocrinologist and the paediatric surgical team, after complete disclosure of all relevant clinical information and all available options have been discussed and after informed consent has been obtained.
- general principals of surgery for AG has been outlined in the preceding section on AG.
- it is recognized that 46,XX children with significant virilization may present at a later age. Consideration for sex reassignment must be undertaken only after thorough psychological evaluation of patient and family. Surgery appropriate to gender assignment should be undertaken after a period of endocrine treatment.

Psychological issues

- females with CAH show behavioral masculinization, most pronounced in gender role behavior, less so in sexual orientation, and rarely in gender identity.
- even in females with psychosexual problems, general psychological adjustment seems to be similar to that of females without CAH.
- currently, there is insufficient evidence to support rearing a 46,XX infant at Prader stage 5 as male.
- decisions concerning sex assignment and associated genital surgery must consider the culture in which a child and her/his family are embedded.

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