ENDOCRINE PROBLEMS IN CHARGE FOR THE PHYSICIAN

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Although genital anomalies are common in CHARGE and make up part of the diagnostic criteria (minor criteria), there are few data on their management and outcomes, especially long-term. As a result much of the data is anecdotal, and recommendations are therefore based more on experience in groups of children with other similar anomalies. Recent studies have however confirmed delayed or absent puberty (more so in boys than girls) Blake et al., 2005.

TYPE & FREQUENCY OF GENITAL ANOMALIES IN CHARGE SYNDROME

	Frequency
Males:	
Micropenis	85%
Undescended testes	60%
Females:	
Hypoplastic labia	Very common
Delayed/arrested puberty (males and females)	Very common
Infertility	Unknown

STUDIES TO CONSIDER

It is thought that the majority of children with CHARGE have isolated hypogonadotrophic hypogonadism (i.e. pituitary gonadotropin deficiency) to account for their genital anomalies. For instance, although a number of different factors are involved in the descent of the testes and the development of the penis, it is clear that gonadotropins (mediated through testosterone) are required. Investigation is therefore aimed at:

- Assessment of gonadotropin function.
- Assessment of gonadal dysfunction arising from:
    1) Gonadotropin insufficiency
    2) Undescended testes in males

INFANTS

Postnatally normal infants show a rise in LH, FSH and testosterone in males and estrogen in females which peaks at 8 weeks and subsides by 6 months. This "mini-puberty" offers a window of opportunity to investigate these children using baseline bloods alone in the six months of life. In males a peak serum testosterone concentration over100 ng/dl can be regarded as normal.

CHILDHOOD & ADOLESCENCE

Between the ages of 6 months and the onset of puberty the levels of gonadotropins, testosterone and estrogen remain low. At this age the following tests are recommended:

1. LHRH (GnRH) stimulation test, looking at pituitary gonadotropins (LH & FSH).

2. hCG test (in males only). Human chorionic gonadotropin – equivalent to LH, tests Leydig cell function alone. There should be a three-fold rise in testosterone following the injections; the response reflects the amount of functional testicular tissue.

3. For girls pelvic ultrasound should be used to assess the internal genitalia, and the response to therapy.

4. Where appropriate, tests of other pituitary hormones may be performed, such as baseline T4, T3, TSH, 9 am cortisol, prolactin, insulin-like growth factor-1 (IGF-1) and its GH-dependent binding protein (IGF-BP3), electrolytes and plasma/urine osmolality.

5. Formal anterior and/or posterior pituitary function.

THERAPY

<u>Micropenis</u>

If the underlying cause is thought to be hypogonadotrophic hypogonadism, then the treatment is testosterone replacement. This can be given by intramuscular injection (testosterone enanthate or propionate 12.5-25 mg 3-4 weekly for 3-4 doses). Topical testosterone cream 2% is also available and is administered once or twice daily for up to 3 months. Absorption may be erratic and (especially if female) the person applying the cream must ensure that they wear gloves. Some pubic hair growth may occur after testosterone administration. The most important single predictor of adult penile size appears to be the initial length of the penis.

It is unlikely that hypoplastic labia need any therapy.

Cryptorchidism

The optimum timing and mode of therapy to bring down the undescended testis is contentious, even in "normal" boys. Histological changes occur in the cryptorchid testis within 1-2 years, although this must be balanced against the increased technical difficulties of surgery at younger ages. Even if the testes are not felt to have much potential for function, many surgeons would still perform orchidopexy to reduce the chances of detection of malignant change.

Hormonal therapy with hCG (human chorionic gonadotropin) may be appropriate (especially for palpable testes), and is usually given after the age of four years (with a 50% success rate). Traditionally 500-1000 IU is given intramuscularly twice weekly for 5-6 weeks. This may also cause increased penile growth as well as producing testicular descent.

Delayed/absent puberty

MALES

- Intramuscular testosterone enanthate or propionate, 50-250 mg monthly.
- Oral testosterone undecanoate 20-120 mg daily.
- Patches and long-acting subcutaneous pellets have been used in hypogonadal boys with some success.

Starting with low-dose oral testosterone (eg testosterone undecanoate (Restandol)) 40 mg alt die offers more flexibility initially in titrating/stopping if there are problems such as worsening behaviour.

FEMALES

- Ethinyloestradiol initially 2 mcg/day, increasing over approximately 2-3 years to 10 mcg/day. When full pubertal progression has occurred or if there has been breakthrough bleeding then change either to low dose oral contraceptive pill (OCP) or adult HRT.

CAVEATS

- Testosterone can cause fluid retention and should be used in caution in children with heart failure.
- As hCG testing only investigates the Leydig cell function of the testis, an absent response does not therefore necessarily confirm that there is no testicular function.
- hCG should not be used in girls as it can cause ovarian hyper-stimulation.

- Although relatively rare, hypopituitarism may also occur in CHARGE, and the following may indicate that further investigation of the other pituitary hormones is required:

  - Other midline defects such as clefting.

  - Conjugated hyperbilirubinemia in the neonatal period.

  - Hypoglycemia in the neonatal period.

  - Absence/hypoplasia of pituitary or other midline structures on brain scanning.

- Animal studies have suggested that early exposure to exogenous testosterone may down- regulate the androgen receptor, leading to poor penile size in adulthood. This has not been shown in human disorders where there is early exposure to androgens.

- There are concerns regarding long-term oral testosterone therapy as this has been shown to cause liver dysfunction in some patients.

- If the testes are retained intra-abdominally it is highly unlikely that fertility can be achieved, and even if the testes are brought down then fertility is likely to be compromised. It is also recognized that the risk of malignancy is higher in those with previously cryptorchid testes.

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GENITAL/ENDOCRINE PROBLEMS IN CHARGE SYNDROME: PARENT INFORMATION

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GENITAL ABNORMALITIES SEEN IN CHARGE

Although genital abnormalities (minor diagnostic criterion) are common in CHARGE, there is very little information in the literature describing these problems or treatment. More importantly, as children may have other potentially more serious problems (especially at birth) the genital abnormalities are often not noted or treated.

In both sexes with CHARGE the main problem seems to be an abnormality in production of the hormones (chemical messengers) from the pituitary gland (a small pea-sized gland lying underneath the brain) which control the production of sex hormones from the testicles in boys, and ovaries in girls. This can result in:

- In boys, undescended testicles (one or both) and small penis (micropenis - less than 2.5 cm (1") stretched length) at birth. About three-quarters of boys with CHARGE will have micropenis. About half will have undescended testes. Both problems are due to the fact that descent of the testicles into the scrotum and growth of the penis in the last part of the pregnancy are dependent on the production of the hormone testosterone from the testicles (under the influence of pituitary hormones).

- In girls, the clitoris and labia minora (inner vaginal lips) may be smaller than usual, but this will not be as obvious as in the boys. It is very common in girls with CHARGE.

- In both sexes, failure or slow progress in puberty is very common, more so in boys than girls. This will mean that the boys will not get increase in the size of their testicles and penis, and the girls will not develop breasts or begin their periods without hormone treatments. In both sexes, there will be failure of development of pubic and axillary (armpit) hair.

- Infertility. The outlook for fertility in children with CHARGE is unknown.

TESTS WHICH MAY BE RECOMMENDED

BASELINE BLOOD TESTS

These measure the amount of hormones in the blood, either on a single sample (baseline levels) or after the levels are stimulated (usually by a chemical or hormone injection). The testicles and ovaries are both quite active in the months before and after birth, and baseline levels may be quite helpful. From about six months of age until puberty the production of sex hormones is very low, and therefore it is often necessary to measure hormones after stimulation.

- LH (luteinizing hormone) produced from the pituitary gland is responsible for the production of testosterone in boys, and for the production of estrogen and progesterone in girls.

- FSH (follicle stimulating hormone) produced from the pituitary gland is responsible for assisting in the production of sperm in the male, and ovulation in the female.

- Testosterone, the male sex hormone, produced from the testicles.

- Estrogen, the female sex hormone, produced from the ovaries: this causes breast development.

- Progesterone, another female sex hormone from the ovaries, when present along with estrogen produces menstruation.

STIMULATION TESTS

- LHRH test. In this test the production of LH and FSH from the pituitary gland is measured using luteinizing hormone releasing hormone (LHRH) as the stimulatory hormone. This is usually done over one hour, with samples taken after 0, 30 and 60 minutes after intravenous injection of LHRH. In most patients with CHARGE there is little or no increase in LH & FSH during the test.

- hCG (human chorionic gonadotropin) test. By giving several injections of a substance similar to LH over several days, this measures the ability of the testicle to produce the male hormone testosterone.

Although hCG will also stimulate hormone production in girls it may cause ovarian over-stimulation and is therefore not usually used in girls.

IMAGING

In girls ultrasound can be used to assess the size of the ovaries and uterus (womb).

In boys ultrasound may be used to assess the position of the undescended testicles, although other scans (CT, MRI) may be more accurate.

TREATMENT

UNDESCENDED TESTICLES

If the testicles are undescended they need to be brought down. This is usually done surgically, requiring one or more operations. Ideally this should be done as early as possible, although other medical problems of CHARGE and technical difficulties of performing surgery in young babies usually means that it is performed when they are older. Alternatively, the testicles can sometimes be brought down using hCG injections (usually twice weekly over 3-6 weeks), and there is some evidence that it works best in testicles which are not completely undescended, and after 4 years of age.

MICROPENIS

A penis which at birth is less than 2.5 cm (1") (stretched) is defined as a micropenis. This should be treated with testosterone. This can be given as a cream applied twice daily for up to three months. As it is absorbed through the skin, the person applying it should wear gloves. Alternatively, testosterone injections can be given monthly for 3-4 months. Although there have been theoretical worries that early treatment will affect the growth of the penis during puberty, this does not appear to happen. *Testosterone can cause fluid retention and should be used in caution in children with heart failure*.

The small labia in girls are not usually treated.

DELAYED PUBERTY

Although there may be worries about worsening behavioral problems during teenage years by treating with sex hormones, this must be balanced against the long-term risks of osteoporosis. The timing of treatment will take into account the normal age of puberty in boys and girls (from 11 years of age), but may be delayed to see if puberty occurs spontaneously.

GIRLS: Gradually increasing doses of estrogen in tablet form is used. Once full pubertal development has occurred, adding in progesterone either as hormone replacement therapy (HRT) or in the low-dose oral contraceptive pill (OCP) will produce periods if the uterus is of sufficient size.

BOYS: Gradually increasing doses of testosterone are given by injection, tablet or patch.

In both sexes it is likely that hormone replacement will need to be given long-term.