CHARGE syndrome; the R and the G
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That growth and genital problems are an important part of CHARGE syndrome was recognised in their inclusion in the original description. In CHARGE the R stands for retarded growth and (development), and G for genital abnormalities.

These processes are not only under the control of nutrition (food) but also hormones, chemicals produced from specialised glands, which are released into the bloodstream and carried by it to other parts of the body to produce their effect. There are several different hormones involved in growth and puberty, and unfortunately many of them are affected in CHARGE!
GROWTH

There are 3 growing phases, all of which are under different controls. These phases are:

*Infantile:* This occurs during the first 2-3 years of life, and is almost completely dependent on nutrition.

*Childhood:* This occurs from ~2 years of age until puberty, and is dependent on both nutrition and also hormones including growth hormone.
**Puberty:** From puberty onward, this phase is under the control of growth hormone and sex hormones acting together.

All of these phases are affected in CHARGE, which results in around \(\frac{3}{4}\) of children having heights and weights below the normal range, with reduced final height in many.

**Infantile:** many babies with CHARGE have low birthweight or length, and failure to thrive after birth is common as around 90% have feeding problems, which can be either mechanical (choanal atresia/stenosis, cleft lip and/or palate, tracheo-oesophageal fistula) or abnormalities in nerves involved in swallowing (cranial nerves VII, IX, X.)

**Childhood:** children can grow normally during childhood, although they are often small. Poor growth, especially if they are getting adequate calories should raise the question of an underlying hormone problem.

**Puberty:** Either failure to enter puberty (delayed/absent), or getting only part way through (arrested) is very common in CHARGE, especially in boys, few of whom enter puberty on their own, whilst up to \(\frac{1}{2}\) of girls do.
As a result we would recommend that all children with CHARGE are seen by a multidisciplinary team including a paediatrician with expertise in growth and hormonal problems (paediatric endocrinologist), ideally throughout childhood, and into adulthood. At each clinic the following should be measured and plotted: height, weight, weight for height (body mass index), head circumference in younger children and puberty assessment in older patients. Additional information on height potential also can be obtained by measuring parents heights to produce a genetic target height, and assessing remaining growth by performing a “bone age,” looking at the growing ends of the bones in a left wrist X-ray. Apart from assessing nutrition eg. calcium and Vitamin D levels, blood levels of hormones may also be checked, either on a single blood test eg. thyroid, growth factors (IGF-1/IGF-BP3), although as some hormones are not produced in a constant fashion then a day case admission for stimulation testing may be required. This is commonly done to assess growth hormone,
stress hormones (cortisol), and sex/puberty hormones.

**Growth hormone therapy**
Some children with CHARGE syndrome have been treated with injections of growth hormone in order to try and improve not only short term growth but also final height. Many (~75%) of these children were growth hormone deficient, but this may reflect the fact that they are more likely to be treated than children who are not. Data on several dozen growth hormone treated children with CHARGE from Europe and also the USA has shown initial good response, although there is little long-term data.

**Genital abnormalities**
These are present at birth, and as the hormones involved in genital development and puberty are the same may give a pointer to possible future problems in puberty. Indicators are:

**Boys**
- Micropenis (penis smaller than 1 inch at birth): Present in 85%
- Undescended testicles (one or both): Present in 60%.

Girls
- Small inner lips (labia) probably very common.

Hormone testing can involve single blood tests (testosterone in boys, oestrogen in girls) but also commonly includes testing of the hormone drive of the hypothalamus and pituitary using the LHRH (GnRH) test, as this is often deficient in CHARGE (hypogonadotrophic hypogonadism), and in boys the hCG test which tests the ability of the testicles to produce male hormone. Girls may also have an ultrasound looking at the uterus (womb) and ovaries. These tests are often done shortly after birth when there is a “mini-puberty” and also from 10-11 years of age.

Our experience in Birmingham is that many girls show normal hormone responses, whilst these are significantly reduced in boys both at birth and also puberty.

Micropenis is treated with the male hormone (testosterone) either given by monthly
injection or daily cream. Undescended testicles usually need to be brought down surgically, and if the child is having repeated operations this is usually done at the same time to avoid extra anaesthetics. Hypoplastic labia don’t need treatment.

Delayed puberty

Is it delayed, absent or arrested? The definition of delayed puberty is absence by 13 years in a girl, 14 in a boy. As these pubertal hormones are involved not only in the physical changes of puberty but also the puberty growth spurt, patients with delayed puberty will not only show absence of puberty signs but also poor growth and short stature in teenage years. NB: Absent sense of smell (anosmia) now appears to be a pointer to pituitary puberty hormone problems. NB: Remember that some sex hormones arise from the adrenal glands which lie above the kidneys, so pubic or armpit hair alone, spots, greasy hair and skin, adult body odour and adolescent mood swings may not necessarily be puberty!

Testing is the same as in genital abnormalities ie.
Baseline “one-off” bloods are often not useful: LH, FSH, oestrogen (oestradiol) in girls, testosterone in boys.

Stimulation tests:
- LHRH tests “top end”: hypothalamus and pituitary.
- hCG (in boys) tests “bottom end”: testicles.

Treatment involves sex hormone replacement in gradually increasing doses to mimic normal puberty:
- In boys testosterone given by injection, tablet or gel.
- In girls oestrogen given by mouth, and then usually the oral contraceptive pill which contains both oestrogen and the other female hormone progesterone. To avoid frequent and distressing periods, the packs can be run into each other with withdrawal bleeds only 2–3 times per year rather than monthly.

Whilst many parents are concerned about giving sex hormones to children with CHARGE because of concerns about worsening behaviour, inappropriate sexual
behaviour, menstrual bleeding (in girls), persistent erections (priapism) in boys, this must be balanced against the risks of long-term osteoporosis (brittle bones), as most bone strength is laid down in the mid to late teens under the influence of sex hormones, and then steadily lost after that. Every 10% increase in bone mass is equivalent to a 50% reduction in fracture rate.

Although other factors such as calcium and vitamin D are important neither on their own will prevent osteoporosis, and so we do give sex steroid therapy to all adolescents with CHARGE, which is usually well tolerated, and if problems arise with gel or tablets the dose can be rapidly cut back. The bone scans (DEXA) do require specialist interpretation to take into account other factors such as short stature which may overestimate osteoporosis, although studies on adults with CHARGE do indicate that bone strength is significantly reduced especially if sex hormone therapy has been delayed or not given.

References