Congenital adrenal hyperplasia 21

Key facts

- Congenital adrenal hyperplasia (CAH) is a group of inherited disorders that result in impaired hormone production from the adrenal glands.
- The most common form of CAH is caused by a deficiency of the enzyme 21-hydroxylase (21-OHD). This accounts for over 90% of people with CAH.
- In 21-OHD deficiency, virilisation occurs because of increased production of male sex hormones by the adrenal glands. Excessive loss of sodium in the urine (salt wasting) can occur because of inadequate production of the hormone aldosterone.
- CAH can present shortly after birth with severe vomiting, failure to thrive and dehydration, and can be a life-threatening condition if not recognised and treated.
- In all forms of the condition, health, fertility and lifespan can be restored to normal through the use of appropriate hormone replacement therapy.
- 21-OHD is an autosomal recessive condition caused by alterations (mutations) in the *CYP21A2* gene on chromosome 6.

Clinical features

- The condition is extremely variable and depends on the level of impairment of production of cortisol and aldosterone.
- 21-OHD is divided into a classic form with severe enzyme deficiency, and a non-classic form with mild enzyme deficiency.
- The severity of CAHs often correlates to the specific genetic alterations in an individual with the condition.
- Classic 21-OHD presents in females with prenatal onset of virilisation, including ambiguous genitalia. Classic 21-OHD is further sub-divided into the salt-wasting form (about 75%) and simple virilising form (about 25%).
- As newborns with salt-wasting CAH due to 21-OHD present with life-threatening vomiting and shock, prompt diagnosis is imperative.
- The non-classic form of 21-OHD presents post-natally with signs of hyperandrogenism; females with the non-classic form are not virilised at birth.

Diagnosis

- The diagnosis is made biochemically by testing for raised 17-OHP, raised testosterone and possibly elevated renin.
- Genetic testing (see below) can be useful for predicting the clinical phenotype.

Genetic basis

- 21-OHD CAH is inherited in an autosomal recessive manner.
- *CYP21A2* is the only gene known to be associated with 21-OH deficiency. About 40 different genetic alterations (mutations) have been identified; the 10 most common alterations account for about 70% of cases.

Clinical management

- Prompt diagnosis is crucial in order to initiate appropriate therapy with glucocorticoids and/or mineralocorticoids, and to stop the effects of their deficiency.
- Investigations following initial diagnosis aim to:
    1. assess for salt wasting;
    2. distinguish classic and non-classic forms of the condition;
    3. assess the degree of prenatal virilisation in females; and
    4. assess the degree of postnatal virilisation in both males and females.
- Individuals with ambiguous genitalia need to be seen by a multi-disciplinary team, with the input of specialists in paediatric endocrinology, paediatric urology/surgery, clinical genetics and clinical psychology.
- Patients with CAH should wear or carry a medical alert identification specifying adrenal insufficiency.

Management of CAH during pregnancy

- Prenatal treatment of affected female fetuses to reduce the risk of virilisation is possible by mothers taking dexamethasone early in pregnancy.
- Dexamathosone treatment needs to be started before 8 weeks in the pregnancy to prevent virilisation.
- The risks and benefit of dexamethasone treatment need to be discussed with the patient.
- Fetal sexing via free fetal DNA from maternal plasma can be carried out in early pregnancy. This allows dexamaethasone treatment to be stopped in pregnancies that are predicted to be male.

Genetic testing

Indications for genetic testing and genetic counselling include:

- for the purpose of family planning and management in pregnancy;
- to provide information about the genetic status of relatives through carrier testing;
- to offer prenatal genetic diagnosis;
- prenatal treatment of affected female fetuses to reduce the risk of virilisation is possible by mothers taking dexamethasone early in pregnancy.

Genetic testing is available in the UK and usually provided through specialist clinics or regional genetic centres.

This information is intended for educational use and was current in March 2015. For clinical management, it is recommended that local guidelines and protocols are used.