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, accounting for over 90% of cases, is caused by a deficiency of the enzyme 21-hydroxylase (21-OHD).
- 21-OHD is an autosomal recessive condition caused by variants in the *CYP21A2* gene on chromosome 6.
- In 21-OHD deficient individuals, 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 with appropriate hormone replacement therapy.

Clinical features

- The clinical features of the condition are extremely variable, and depend on the impairment level of cortisol and aldosterone production.
- 21-OHD is divided into a classic form with severe enzyme deficiency, and a non-classic form with mild enzyme deficiency.
- The severity of CAH often correlates to the specific genetic variants 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 postnatally 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 and genetic testing

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

- 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; and
  - to provide prenatal treatment of affected female fetuses to reduce the risk of virilisation.
- Genetic testing is available across the UK and usually provided through specialist clinics or regional genetic centres.

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:
  - assess for salt wasting;
  - distinguish classic and non-classic forms of the condition;
  - assess the degree of prenatal virilisation in females; and
  - 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

- If mothers take dexamethasone early in pregnancy, it is possible to reduce the risk of virilisation in female fetuses affected by CAH.
- Dexamethasone treatment needs to be started before eight weeks in the pregnancy to prevent virilisation.
- The risks and benefits of dexamethasone treatment need to be discussed with the mother.
- Fetal sexing, via free fetal DNA from maternal plasma, can be carried out in early pregnancy. This allows dexamethasone treatment to be stopped in pregnancies that are predicted to be male.

Direction to further reading, guidelines and patient groups

Patient support group: https://www.livingwithcah.com/

This information is intended for educational use and was current in December 2019. For clinical management, it is recommended that local guidelines and protocols are used.

Produced in collaboration with Birmingham Women's NHS Foundation Trust's Clinical Genetics department and reviewed by Imperial College Healthcare NHS Trust.