CONGENITAL ADRENAL HYPERPLASIA (CAH) due to 21-HYDROXYLASE DEFICIENCY

CAH is a group of inherited conditions in which patients have an inborn ("congenital") enlargement ("hyperplasia") of the adrenal glands. The adrenal glands are two small structures localized on top of the kidneys in the abdomen. The adrenals are endocrine organs which secrete hormones into the blood. Hormones are substances carrying messages to other organs and are important regulators of many processes such as behaviour, body homeostasis, metabolism, body composition and sex development. The inner part of the adrenal gland secretes the stress hormones adrenalin and noradrenalin. These hormones are involved in response to fright (Fig. 1). The outer part secretes three different steroids hormones: which is important in controlling the blood and also in helping the body combat stress, due to infection or serious injury. 2. which regulates the loss of salt in the urine, androgen, male sex hormone (secreted in both sexes).

Cause

CAH due to 21-hydroxylase deficiency is the most common form and accounts for about 95% of cases. It is an inherited defect in the production of cortisol and aldosterone. This results in lack of aldosterone, which is produced in about two-thirds of patients also of aldosterone, due to an impairment of the enzyme (a protein that catalyses specific reactions) 21-hydroxylase. The low level of cortisol in blood stimulates the pituitary gland (which is located at the base of the brain) to secrete the hormone ACTH (AdrenoCorticoTrophic Hormone) in an attempt to restore the level of cortisol to normal (Fig. 2). Because of the block in production of cortisol this does not occur but stimulation causes enlargement of the glands and an excessive production of male sex steroids (androgens) (Fig 3.). This birth and the high level of androgen causes girls to virilised with enlargement of the clitoris and different partial closure of the vaginal opening. Since boys are masculinised by their testes they show no genital abnormalities at birth. In many but not all children with CAH the lack of aldosterone results in excessive loss of salt in the urine after birth. If this may become critical in the first two or three weeks of life and result in a potentially fatal 'salt-losing crisis'. The increased ACTH also cause some pigmentation of the skin. In the most cortisol deficiency can lead to low blood sugars, but leads the diagnosis than genital abnormalities in girls and salt losses in both sexes.

Fig 1. Structure of the adrenal gland. The outer part (cortex) consists of three layers specifically producing different steroid hormones. The inner part (medulla) secretes adrenalin and noradrenalin (catecholamines).

Fig 2. The production of cortisol and adrenal sex hormones (DHEA, androstendione) are closely controlled to avoid under- or overproduction. ACTH, a pituitary hormone, stimulates the adrenal cortex to make cortisol. Once enough cortisol is produced, it will reduce ACTH production (see red lines with "-".). This system can be compared to a heating system in a house, where the pituitary is the thermostat and the adrenals the radiators. When enough heat (cortisol) is produced, this feeds back to the thermostat (pituitary) and regulates the heat production.
Inheritance.

Congenital adrenal hyperplasia due to 21-deficiency affects about 1 in 12,000 live births in European populations however it does vary between different populations and is more common in inherited condition through alterations in the gene that code for 21-hydroxylase. It is a disorder that means that you need to inherit a from both parents, who are carriers. Parents are as they have one normal copy. All genes are carriers one gene for the structure of the 21-enzyme is abnormal and one is normal; adequate 21- hydroxylase are produced. Children with CAH abnormal genes, one inherited from each parent, normal enzyme is produced. Statistically one in of carrier parents can be expected to inherit both genes and have the disease, two will be carriers inherit two normal genes. Thus, in this type of for parents who have produced a child with CAH, subsequent child has a 1 in 4 risk of inheriting the When a person with CAH has a partner, there is an to have a child with CAH compared to the general and it should be tested if the partner is a carrier the general population is 1 in 50). In case the a carrier, all the children will inherit one abnormal affected parent (who has two abnormal copies) balanced by the normal gene from the other the children will be carriers but none will have the CAH both the degree of virilisation and the salt loss are variable but correlated well with the gene changes. Thus, in most families affected have a similar clinical presentation of the

Treatment.

Patients with CAH cannot produce enough steroid hormones and therefore need to take medicines to make up for it. During childhood, patients with CAH due to 21-hydroxylase deficiency require treatment with a drug called “hydrocortisone”. Hydrocortisone is given in a dose which reduces ACTH secretion and so prevents the excessive production of androgens. Patients with salt loss also need a drug called “fludrocortisone”, a steroid with a salt-retaining action, to replace the missing aldosterone.
The treatment goal is normal growth and development as well as prevention of health problems in later life. However, to meet the balance between too little or too much steroids is the major challenge for the treatment of congenital adrenal hyperplasia. However, too much hydrocortisone causes weight gain and slowing of growth; too much fludrocortisone may cause high blood pressure. On the other hand, patients that are given too low doses can become dangerously unwell because their body cannot respond to stress, and they can develop signs of too high levels of male hormones. As the correct dose of these drugs varies from patient to patient, it is important to monitor the treatment regularly clinically (by checking development of growth, weight, blood pressure and other physical signs) and biochemically (with a blood test) to avoid side-effects of under- or overreplacement with these steroids.

**Emergencies.**

In a healthy person, the body is able to increase levels of cortisol if needed, e.g. during illnesses, operations or other stressful situations. Patients with CAH are unable to do this. It is therefore necessary to mimic the response of the body to stress by increasing the dose of hydrocortisone to cover serious illness or injury (including surgery). Parents need to double or triple the usual dose of hydrocortisone if the child is seriously ill or has an accident. If the dose of hydrocortisone is repeatedly vomited it MUST be given by injection. All families with an affected child must have an injection of hydrocortisone available and know how to give it. In addition some patients may have the tendency to low blood sugars during severe illness due to possible additional problems with catecholamine production. In such individuals extra carbohydrates or dextrose should be given during such episodes.

**Prenatal diagnosis and treatment.**

In a family with one affected child, by genetic testing on placental cells it is possible to determine whether an unborn baby is affected. Since the condition can be treated successfully and is compatible with a fully normal life, termination is not appropriate but it is now possible to give a steroid (dexamethasone) which crosses the placenta and prevents virilisation of a female fetus. If you wish to consider this option it is essential to have preliminary tests done before conception and then to start treatment as soon as pregnancy can be confirmed. See the separate sheet about prenatal treatment.

**Future outlook**

Patients with CAH usually have to take lifelong steroid medication. The evidence suggests that if well treated during childhood most patients with congenital adrenal hyperplasia will reach a normal height but probably a little shorter than would have been predicted if they had not had the disorder. Maintaining the right balance of steroids is important during adult life to avoid the complications of osteoporosis, obesity and hypertension. Fertility is reduced in some patients but there are an increasing number of options for helping patients achieve fertility. An important phase is the transition from paediatric into adult care, which should happen in a well structured process. The condition will require individualised management and treatment requirements can change during life.

© 2011 British Society for Paediatric Endocrinology and Diabetes