Managing Congenital Adrenal Hyperplasia in Childhood

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Dr Jeremy Kirk gave a detailed overview of Congenital Adrenal Hyperplasia (CAH).

CAH occurs in about one in every 15,000 live births, and is the commonest identifiable cause of ambiguous genitalia (where the external genital organs are not clearly male or female). To begin with Dr Kirk described the anatomy of the adrenal glands and the genital organs involved in the condition. There are a number of causes, but the commonest underlying abnormality is a defect in the formation of adrenal steroids (chemical messengers that help to regulate a number of body functions). The adrenal gland produces three types of steroids: glucocorticoids (such as cortisol), which are important in the stress response and maintaining blood sugar, mineralocorticoids (such as aldosterone) which regulate the body’s salt balance, and androgens (or sex steroids) which are also produced in the gonads. They are all produced from cholesterol, and a number of different pathways and enzymes produce the steroids.

He compared the enzyme defects causing CAH to roadworks on a motorway blocking one or more lanes (dependent on the enzyme block). The cholesterol derivatives are cars coming down the motorway, and when they are blocked by roadworks they take a detour down side roads instead. These “side road” enzyme pathways lead to other steroids, i.e. androgens. However the RAC man counting the cars further down the motorway doesn’t know about the roadworks and asks for more cars to be sent down the motorway. Because of the roadworks more cars are sent down the side roads and as a result even more androgens are produced.

When we replace mineralocorticoids and glucocorticoids, the “RAC men” counts these, stops asking for more cars and the androgen supply slows down.

CAH can be diagnosed at any time of life, with different underlying conditions presenting at different ages. At or soon after birth babies (females) may be noted to have ambiguous genitalia or both sexes can become suddenly unwell with a salt-losing crisis. Some present later in childhood with precocious puberty (more properly
pseudo-puberty, since the testes in boys aren’t enlarged), and finally CAH may only be discovered in adulthood as a cause of polycystic ovaries.

External genitalia are identical in the early stages of development of the foetus in the womb. In the absence of other signals they develop as female organs (clitoris and labia), but under the influence of genes and androgens male organs (penis and scrotum) develop. When CAH is suspected soon after birth a full evaluation is necessary. This should include a family history, physical examination (once, by the most senior staff member), ultrasound of internal reproductive organs and adrenal glands, chromosome analysis (to confirm the sex of the baby), and a rapid and reliable measurement of adrenal steroid hormones (e.g. 17-hydroxyprogesterone). Urgent specialist medical advice should be sought, and referral to a multidisciplinary team of a paediatric endocrinologist, surgeon, psychologist and geneticist. The family should be involved at every stage of the process. It is vital to ensure that parents have a good early relationship with the child, and doctors and other staff involved in the care should emphasise that while there may be some problems, the baby is otherwise lovely and healthy.

The aims of treatment are:

1) to replace the deficient steroids

2) to minimise excess steroid production

3) to avoid over-replacement of steroids

4) to minimise virilisation

5) to monitor and aim for optimal height

The treatment and follow up should be coordinated by a regional multidisciplinary specialised service and not by local or district hospital-based general paediatric services.

Hydrocortisone is usually given at a dose of 10-15 mg per m² per day, given in two or three doses. There is some evidence that three doses is ideal, but two can be more pragmatic and ensures better adherence. When the child has reached his or her final height, treatment can be changed to once-daily prednisolone or dexamethasone, although many units still use hydrocortisone. Fludrocortisone (a synthetic mineralocorticoid) is used at about 150 µg per m² per day as a single daily dose. It will only work in combination with hydrocortisone. Salt supplements are usually needed in babies and infants for the first 18 months of life, since they tend to lose salt through the kidneys despite adequate fludrocortisone treatment.

The assessment of treatment is difficult. Monitoring growth is essential, and annual bone age assessment can help to assess androgen effects on the skeleton. Biochemical monitoring assesses the effect of steroid replacement on correcting the adrenal glands own steroid production. 17-hydroxyprogesterone (17-OHP) is a very sensitive indicator of adrenal activity, and changes very quickly in response to steroid doses. Serial measurements over a 24 hour period (usually done by taking “blood spot” tests at home, rather than taking frequent blood tests) often show low levels at night, with
very high levels early in the morning. Androstenedione and testosterone do not change rapidly and are therefore better at monitoring overall long-term control. ACTH is the hormone that stimulates the adrenal gland, and is raised in untreated CAH (that is the effect of the “RAC men” ordering more cars to be sent down the motorway). Renin is another signalling hormone that can be used in CAH monitoring. However testing ACTH and renin levels is practically very difficult and is expensive. Blood sodium (salt) levels are checked regularly.

Every parent’s worry is the CAH crisis, and what to do in the event of illness or accident. For the vast majority of illnesses, such as fevers, bad colds and severe diarrhoea, all that is required is to increase the dose of hydrocortisone (usually 2-3 times the normal daily dose) during the period of illness. If the child is vomiting, this can prevent the extra steroids from being absorbed. Hydrocortisone is absorbed very quickly in the stomach, and if vomiting occurs more than 30 minutes after a dose of hydrocortisone, then the drug is likely to be already in the system. Hydrocortisone suppositories are an alternative for patients who are vomiting. All patients or parents need to have injectable hydrocortisone available quickly for treating collapse due to illness or injury. Patients should also carry a steroid card, stating the current dose and instructing health care workers what to do in an emergency.

While the above describes the “standard” treatment for CAH, a number of other treatment options do exist or have been considered. Cyproterone acetate is a drug that blocks the effect of the excess androgen steroids produced by the adrenal gland. This can be added if normal treatment doesn’t suppress androgen production enough. Zoladex and Prostap are drugs which inhibit the stimulation of “gonadotrophins” – hormones that in turn stimulate androgen production by the gonads. These can also be used in combination with growth hormone to encourage growth.

Surgery to remove the adrenal glands has also been suggested, on the basis that it may be easier to simply replace adrenal steroids rather than also trying to compensate for the overproduction of androgens. No one at the meeting had had this treatment approach.

The psychological issues surrounding this condition are very important, especially for affected girls. Girls tend to exhibit more male type behaviour (they might be “tomboys”), but don’t seem to have problems with gender identity or sexual orientation. Unfortunately the availability of psychological support services for CAH patients in the NHS is very poor.

Finally Dr Kirk drew our attention to a recent survey of UK CAH services for children, carried out by the British Society for Paediatric Endocrinology and Diabetes (BSPED). Of the 57 units surveyed, only one provided a dedicated CAH clinic (the rest integrating these patients with other endocrinology patients). Combined clinics with adult endocrinologists should ideally exist to ensure smooth transfer to adult services at about 16 years of age, and only three units didn’t provide this service.

Dr Kirk also directed us to some useful information sources:

www.bsped.org.uk Useful patient information
http://jcem.endojournals.org/cgi/content/full/87/9/4048 European consensus document