ADULT MANAGEMENT OF CONGENITAL ADRENAL HYPERPLASIA

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Professor Stewart began his talk by describing his practice in Birmingham, where he has approximately 60 adult patients with CAH under follow-up.

Cortisone acetate was introduced into the UK in 1953 and therefore the longest surviving salt wasting CAH patient is 53 years old.

He then reviewed the ACTH axis as previously discussed by Dr Kirk. 21 hydroxylase deficiency accounts for about 95% of adult patients under follow-up in Birmingham. He briefly described new research looking at genetic mutations. There is good correlation between where the mutation is and severity of disease. Only 1% of enzyme activity allows aldosterone production so preventing salt wasting.

He then outlined the major issues in adults with CAH which include:

1. **Glucocorticoid therapy** – obesity and short stature, decreased bone density, prevention of crisis

2. **Mineralocorticoid**
3. **Gonadal dysfunction and low fertility**
4. **Psychosexual dysfunction in women.**
5. **Lost to follow-up**

**1. Which glucocorticoid should be used in adults?**

There is no consensus opinion and no real evidence base. Cortisone acetate was the first available steroid but needs to be metabolised by the liver before becoming an
The first choice of steroid replacement in the UK is hydrocortisone, while in the USA prednisolone is used more than in the UK and dexamethasone is generally felt to be too potent for routine use. A US survey found 60% of patients were treated with hydrocortisone, 20% with prednisone and 10-15% with cortisone acetate.

There continues to be difficulty in finding the correct dose. Over-replacement can cause obesity, hypertension, diabetes and osteoporosis (60-70% patients have metabolic syndrome). Fertility issues can occur due to the hormones that regulate ovaries and testes being turned off.

Under-replacement can cause androgen excess, increased danger of crisis and fertility issues (irregular periods, excess hair growth in women due to androgen excess).

In the normal population cortisol levels peak at 4-8am with the nadir being between 8-12pm (diurnal rhythm). Using hydrocortisone you may have very high levels at certain times and then undetectable levels – it is impossible to replicate the normal diurnal rhythm. Hydrocortisone has a short half life of 1½ hours and a dose is cleared within 3-4 hours. The half life of dexamethasone is longer (3-4 hours).

**Which lab test for monitoring in adults**

From a survey of UK endocrinologists the consensus is that androstenedione is the best test in adults as it gives a far better view of long term control. 17OHP has a very short half life (patients with very suppressed 17OHP as children have been over treated).

**2. Mineralocorticoid replacement**

The average dose of fludrocortisone is 100 mcg (0.1mg). Hydrocortisone also has mineralocorticoid activity (40 mg hydrocortisone is equivalent to 0.1 mg of fludrocortisone). Dexamethasone and to lesser extent prednisolone have no mineralocorticoid activity.

The best method of surveillance of mineralocorticoid dose is plasma renin activity. This should be measured once a year and takes an hour to perform. The target is to be within the upper levels of normal range (2 – 2.5).

**Prevention and treatment of crises**

Symptoms and signs of crisis include low blood pressure, abdominal pain – radiating to lower back and thighs (occurs in 80-90% of patients), nausea and vomiting, fever (60% of patients) and in extreme is dizziness and confusion.

Treatment is with intravenous hydrocortisone – 100-200mg per day. Rehydration is required and patient requires cardiac monitoring because of high potassium.

In patients with Addison’s disease 50% of patients in the UK have less than one crisis per year. A small percentage of patients will have multiple crises a year.
In order to prevent crises one needs to try to anticipate the risk of crisis. Patients need to increase glucocorticoid dose during intercurrent illness. Mineralocorticoids do not require increased replacement. In situations of moderate physiological stress e.g. flu / procedure under local anaesthetic the glucocorticoid dose should be doubled. In patients undergoing a general anaesthetic / trauma 100-200mg of hydrocortisone per day intravenously should be given until able to eat and drink (In normal population cortisol levels increase 2-3 fold when having General anaesthetic).

Patient education, the carrying of medic alert and steroid cards is also important.

3. Fertility

Insufficient glucocorticoid can cause testosterone excess which in males can cause sperm arrest due to suppression of FSH and LH. This tends not to be a big problem in men as the testes produce large amounts of testosterone, Adrenal rests within the testes are seen in about 30% of patients on ultrasound scanning, but are rarely palpable. They can be misdiagnosed as testicular tumours.

In women androgen excess causes polycystic ovariies, anovulation, reduced egg production. Prof Stewart runs a joint fertility clinic with a gynaecologist and the majority of his patients achieve pregnancy.

4. Sexuality

Sexual dimorphism of the brain is thought to occur due to high androgen exposure in fetal life. There is some data that girls with CAH girls adopt a more boy-ish approach to childhood activities but whether this impacts on adult sexuality is uncertain. In a Californian study there was evidence of increased homosexuality in women with CAH, but this has not been replicated in other studies.

5. Lost to follow-up:

If medication is not taken correctly massive enlargement of adrenal glands can occur and there is a possible increased risk of malignancy. The risk of crises also increases in patients who do not attend follow-up.

Experimental treatments

A number of experimental treatments were discussed including:

1. DHEA and sexuality - women with CAH given DHEA have reported improvement in sexuality.
2. There is relative adrenal medullary deficiency in CAH. There is limited evidence that giving catecholamines (noradrenalin/ adrenaline) in children increases their ability to cope with stress and exercise.
3. Adrenalectomy – Prof Stewart has two patients who underwent this procedure but residual adrenal tissue has meant both have recurrent disease.
4. Gene therapy – CAH is not a severe enough disease, the risks would outweigh the potential benefits
Prof Stewart then gave an outline of an audit of his Birmingham patients, with data on 40 of 65 patients, ages 17 to 41. The mean height in women was 154 cm and in men 160 cm. Males were 13.5 cm below the mean parental height. 75% of patients were overweight with 50% being obese. There was an increased prevalence of metabolic syndrome.

42% of these patients were married – the same proportion as the normal population. No obvious sexuality problems were highlighted.

There were no major problems with bone density, thought to be due to the negative effect of glucocorticoids being balanced by the positive effect of testosterone.

A National CAH database is in development. The centres involved include:

**England**
- Birmingham - Queen Elizabeth Hospital
- Bradford Royal Infirmary
- Cambridge - Addenbrooke’s Hospital
- Exeter - Royal Devon and Exeter Hospital
- Leeds General Infirmary
- Liverpool - Royal Liverpool University Hospital
- London - University College Hospital London & St Thomas' Hospital, London
- Manchester Royal Infirmary
- Newcastle - Royal Victoria Infirmary
- Oxford - Churchill Hospital
- Sheffield Northern General Hospital or Royal Hallamshire Hospital
- Watford General Hospital

**Northern Ireland**
- Belfast - Royal Victoria Hospital

**Scotland**
- Aberdeen Royal Infirmary
- Edinburgh - The Great Western
- Glasgow - Western Infirmary

**Wales**
- Cardiff - Heath Park

The database aims to recruit more than 250 adult patients with follow-up of at least 10 years. It will look at morbidity and outcome, quality of life, body composition and fertility.