Diagnosis and Management of CAH in the United Kingdom

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Conflict of interest disclosure

• Invited lectures
  – Merck
  – Sandoz
  – Diurnal

• International paediatric endocrine nurse advisory board
  – Merck
Introduction

• What is CAH
• Diagnosis in the UK
  – Newborn screening
  – International practice
• Treatment
• Management
• Education and Support
CAH – reminder of key points

• An adrenal enzyme defect
• Classical 21-hydroxylase deficiency is the most common
  – 1 in 15,000 births in the UK
• Results in glucocorticoid and mineralocorticoid deficiency
  – ↑ ACTH secretion by the anterior pituitary
  – Accumulation of steroid precursors prior to the enzyme defect
  – ↑ androgens production
### Diagnosis

**Boys**
- *Can* have hyperpigmented scrotum and genitalia at birth, but usually look ‘normal’
- **Presentation**
  - Day 5
  - Second week of life
    - Poor feeding, weight loss, failure to thrive
  - If CAH not recognised
    - Salt losing crisis
      - Due to the aldosterone loss

**Girls**
- Genitalia are usually virilized due to excess androgens
  - Allows earlier diagnosis
- Mild clitoromegaly to full masculinisation
  - Prader staging
- DSD service

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![Diagram of genitalia stages](image)
46XX CAH

- Baby will have been exposed to excess male hormone in-utero
- The genitalia will look like a boy’s:
  - Labia will fuse to look like a scrotum
  - Clitoris enlarges and looks like a penis
- Can sometimes be so severe, sex assignment is difficult
  - Need karyotype
  - Will still have normal internal structures
  - Surgery may be needed to correct outer appearance
    • CONTROVERSIAL

- Exposure to prenatal androgens and Prader 3 virilisation at birth
- Same baby at age 8 weeks at the time of genital reconstruction, showing some regression of virilisation after starting steroid treatment
- Another baby girl with a more severe form of 21OHD, leading to more severe virilisation (Prader IV)
Diagnosis

- Confirmed by a raised 17OHP level after day 3 of life
- Salt wasting confirmed by:
  - Low plasma sodium
  - High potassium
  - Increased urinary sodium excretion
  - Virilised girls
    - Chromosome analysis
    - Pelvic ultrasound

- Short synacthen test – IM or IV
  - 0 – 6 months: 62.5mcg
  - 6 months – 2 years: 125mg
  - Over 2 years: 250mcg

- Urine
  - Steroid analysis to confirm the 21-hydroxylase deficiency defect

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<th>Time</th>
<th>Cortisol</th>
<th>17-OHP</th>
<th>11-DOC</th>
<th>A4</th>
<th>ACTH</th>
<th>Renin</th>
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Newborn Screening

- Most countries incorporate screening for CAH in the neonatal period
- UK National Screening Committee (2016)
  - Accuracy of test poorer in babies born early and low birth weight
    - Affected babies may be missed
  - Screening takes place too late to benefit people with some types of CAH
  - Current 17-OHP immunoassay – incorrectly identifies a large number of babies with CAH
- Germany
  - Increased number of false positives (*Fingerhut, 2018*)
    - Suggested changes in their biochemical analysis
International Practice

- **South Africa** *(Ganie, 2018)*
  - 3233 patients in endocrine clinic
    - 44 CAH
      - 60% CSW
      - 46 XY median age 3/12
      - 46 XX median age 1/12
    - 2/3 of the females presented with DSD in neonatal period
    - 1/3 presented later with dehydration and shock
  - Seems to be infrequent in black South African children

- **Nigeria** *(Osifo & Nwashill, 2008)*
  - All children diagnosed with CAH in one centre – 5 year period
    - 27 children
      - 24 female, 3 male
  - Delayed presentation
    - Influenced by cultural beliefs, and lack of awareness
    - Genital abnormality only reason medical consultation in 85%
    - All females mistakenly raised as males
**Management**

**Medical**
- Hydrocortisone 10mg tablets
  - 10 – 15 mg/m²/day
  - Total dose spread 3 – 4 times throughout the day
- Fludrocortisone 100 mcg tablets
  - 150 mcg / m² / day
- Salt supplements
  - Oral salt supplements (until one year of age) in the 5mmol/ml 30% Sodium Chloride solution – 5mmols/kg/day, in 4 divided doses = .......mls per dose four times a day
  - Can stop when fully weaned

**Surgical**
- Should only be performed by experienced surgeons
- Practice
  - 2 – 6 months of age
- Genitoplasty controversial
  - Vaginoplasty
  - Clitoroplasty
  - Labiaplasty

What's it really like to have Adrenal Insufficiency?
Suspension v tablets

- Increased need for higher hydrocortisone doses in children on liquid hydrocortisone
  - Inadequate control of androgens
  - Signs and symptoms of Cushing’s syndrome
    - (Endocrine Society Clinical Practice Guideline, 2010)
  - Hydrocortisone suspension not bioequivalent to tablets
    - (Merke, 2001)
  - Instructions to be given on cutting / crushing tablets
Range of choices and methods to give hydrocortisone


Various methods to administered an oral hydrocortisone dose of 2.5 mg (Watson et al, 2017)
Manipulation of tablets

- Quartering 10 mg hydrocortisone tablets
  - Unacceptable dose variations (Madathilethu et al, 2018)
    - Glucocorticoid excess
    - Cortisol insufficiency

- Splitting tablets
  - Unequal parts / crumbling = unequal doses

- Common practice in the UK
  - Renders the medication unlicensed
  - No guidelines or evidence (Richey et al, 2017)

- Compounded hydrocortisone capsules
  - Variability in capsule content = variation in dose
    (Neumann et al, 2017)
Alkindi Hydrocortisone granules: The future

- Granules well tolerated in children less than 6 years of age
  - Cortisol levels measured
  - Smell and taste are neutral (Neumann et al, 2018)
  - Tested on healthy adults – report no smell or taste (Whitaker et al, 2015)
Alkindi granules – accurate dosing

- The formulation of hydrocortisone with taste masking is based on granule, multi-layered, multi-particulate technology to deliver 0.5mg, 1mg, 2mg and 5mg doses
- Immediate release granules are contained in capsules, which are broken open and the granules administered orally
3. Draw up 2mls of cooled, boiled water into a 2ml syringe
4. Mix the crushed 1/4 of a tablet with the 2mls of cooled boiled water
5. Then draw up 1ml of the mixture to give 1.25mg
6. Give by mouth as shown by ward nurses
Sick day rules

• **Illness**
  – Double the normal Hydrocortisone until well
    • Triple?
    • 4am dose?
  – Guidance for families
    • Fever
    • Antibiotics
    • Vomiting (if within an hour of taking)
    • Diarrhoea
    • 24 hours around administration of childhood immunisations

• **Emergency**
  – Severe D & V
  – Serious injury
    • Unconscious
    • Severe burns
    • Break a limb
  – Administer Emergency injection of Hydrocortisone and / or Glucagel
  – Call an ambulance

If parents / carers think their child is ill enough to be kept home from school

If parents / carers think the child is ill enough to attend an Emergency Department
Sick day and emergency management

- Emergency injection of hydrocortisone and oral glucogel
- Liaise with nurseries
  - Schools when older
- Medic alert jewellery
- Usually dispense x2 emergency packs
  - Home
  - Bag
    - Another when older for nursery / school
Living with CAH

- Give support to families and sufferers
- To increase awareness of the condition to the public and to the medical profession
- To raise funds to support research
  - Regular conferences
  - Family support days
  - Informal meetings
London DSD data over 21 years N=657
DSD families

- dsdfamilies.org
- UK based support group
  - Information and support resource for families with children, teens and young adults with a DSD
  - Links to other support groups throughout the UK
    - CAH, TS, Hypospadias, Klinefelter, AIS
  - Links to international DSD support groups
dsdfamilies.org

• Advice
  – How to talk to others
  – How to talk with teenagers
  – Dilatation

Top Tips for Talking
about differences of sex development
Conclusion

• Awareness of different practices internationally
  – Newborn screening – change in practice
  – Availability of biochemical and molecular analysis
  – Cultural practices
    • Diagnostic data different due to diagnostic procedures
  – Multidisciplinary teams