

Insights into **MAN**aging Growth for **Endocrine** Nurses

12-13 October 2017, Toulouse, France

An Independent Medical Education Event for Paediatric Nurses

Session report



Thank you for attending the 2017 IMAGE meeting and contributing to the discussions. We hope you enjoyed the sessions and have taken away new knowledge that can help you in your practice. This year's meeting began by focusing on adrenal disorders, then moved onto the two important psychological issues of medication adherence and bullying, and ended with a recap and update of the management of growth disorders.

Most of the presentations are available as webcasts at <http://www.excemed.org/live-events/image-2017-insights-managing-growth-endocrine-nurses>. To complement this, we here provide a written overview of the meeting, recapping the plenary presentations and highlighting the key take-home messages.

Congenital adrenal hyperplasia

Ieuan Hughes (University of Cambridge) kicked off the first session with an overview of the most common adrenal disorder encountered in children: congenital adrenal hyperplasia (CAH). The vast majority of children with CAH lack fully functional 21-hydroxylase – the enzyme that converts 17OH-progesterone into mineralocorticoids and glucocorticoids. Instead, 17OH-progesterone is diverted into a pathway leading to its conversion into androgens, resulting in a build-up of androgens, as well as of 17OH-progesterone itself.

CAH is divided into the classic and simple virilising subtypes. The former is very rare and occurs in children with very little or no functional 21-hydroxylase; they present soon after birth with virilisation with or without salt loss episodes, which if untreated are frequently fatal. The simple virilising subtype is much more common, occurring in about one in 500 to 1000 children, who present later in childhood and do not have salt-losing crises.

Age and presenting features in children diagnosed with CAH	
Age at presentation	Clinical features
Infancy	Females: ambiguous genitalia Both sexes: salt loss
Early childhood	Males: virilisation, rapid growth
Late childhood	Females: early pubic hair, rapid growth
Adolescence/young adult	Females: delayed menarche, irregular menses, hirsutism, acne, weight gain, infertility Males: testicular masses

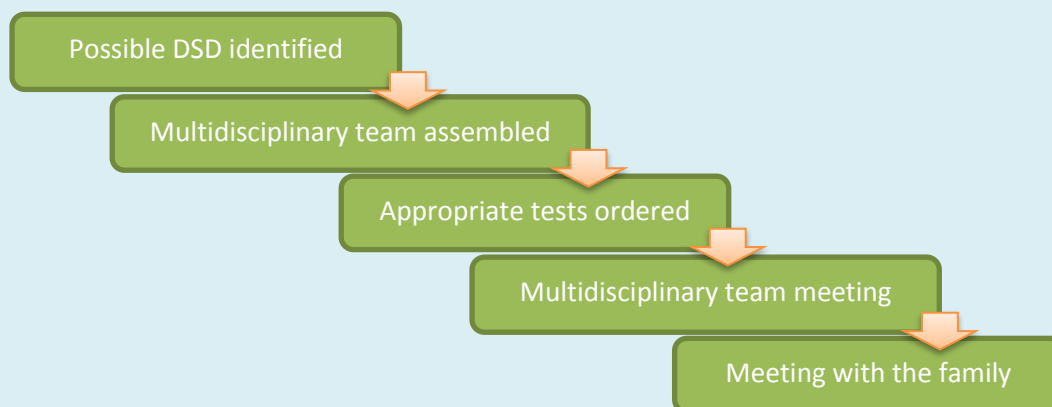
Spotlight: how you can support a family with a new CAH diagnosis

Wendy Schwartz presented the Alberta Children's Hospital (Calgary, Canada) protocol for managing infants with disorders of sexual development (DSD), produced in response to concerns that these cases are not always optimally handled.

Honest and open communication

Starting at the point at which ambiguous genitalia are identified, the protocol requires prompt and honest communication of concerns to the parents by the healthcare provider who identifies the issue. They should use the appropriate medical terms, gender-neutral language and avoid terms such as "abnormal". Providers should encourage parents to delay naming their baby and should encourage bonding.

The care pathway



The care pathway requires the assembly of a multidisciplinary team, which orders the appropriate investigations. ***No individual results should be communicated to the family until all results are available*** and the complete picture has emerged. At this point, there is a team conference, followed by a meeting with the family, at which the baby's gender is assigned.

Offer psychosocial support

Receiving a DSD diagnosis for their new-born child can be very stressful for parents, who will have to grapple with unfamiliar terminology, the perceived stigma of the condition and how to communicate the news to family and friends. The family should therefore be offered psychosocial support, with access to a psychologist the ideal scenario, although this is rarely available.

Diagnosis of CAH requires fluorescence in situ hybridisation to establish the presence of X and Y chromosomes, and measurement of 17OH-progesterone and androgens. Of note, 17OH-progesterone is high in all babies at birth, because of production by the placenta, so testing must be delayed by 24 hours, by which time levels in unaffected infants have declined.

Accurate and early diagnosis is vital in infants at risk of salt loss, but is important even in patients without, because a missed diagnosis results in mis-assignment of sex, which may not be recognised until adolescence. For this reason, it is important to be alert for non-palpable testes in apparently male infants.

Newborn screening can aid detection of early-onset CAH, including the simple virilising forms, but is not available in all countries because of concerns about false-positive results and cost-effectiveness.

Treatment of patients with CAH involves replacement of mineralocorticoids and glucocorticoids. The latter must be given three times daily, although slow-release formulations are undergoing development to

allow a more physiological delivery of hydrocortisone. Glucocorticoid replacement is a particular challenge when patients fall ill and need higher doses to deal with physiological stress, especially if they have nausea or vomiting.

Another challenge of hydrocortisone treatment is achieving the optimal dose, which achieves androgen suppression without compromising growth. Reduced final adult height is common in patients with CAH – although they achieve a height within population norms, they rarely achieve their target based on parental height. *It is therefore important to monitor the growth and bone age of CAH patients.*

The physical manifestation of CAH, ie, virilisation, can potentially be addressed with surgery. However, the difficulty of the procedure varies according to individual patients' internal anatomies, and, although the aesthetic results can be excellent, there may be a payoff between this and patients' later sexual function. This makes surgery something that must be considered on a case by case basis and discussed in depth with the family.

Spotlight: sick day rules

In CAH, and other conditions causing adrenal insufficiency, the body is unable to produce sufficient quantities of cortisol, resulting in a lifelong need for supplementation. Physical illness adds to the challenge, by increasing the body's need for cortisol and potentially resulting in an adrenal crisis if the dose of hydrocortisone is not increased.

Mandy Whitehead outlined the information given to families with new CAH diagnoses at her workplace, the Leeds Children's Hospital, UK. This includes understanding the usual hydrocortisone dose and how and when to administer it, knowing when to increase the dose and how long for, recognising hypoglycaemia, and understanding the additional risks associated with diarrhoea and vomiting.

One important point to communicate to parents is that, if a child is ill outside of regular hospital hours and parents are unsure what to do, they should always err on the side of increasing the hydrocortisone dose, because increasing the dose will do no harm in the short term, whereas not increasing it could lead to adrenal crisis.

To support parents, Mandy's team does the following:

- Offers time, reassurance and support
- Reassures parents that they expect them to have more questions very soon
- Encourages them to try and maintain their normal life
- Phones them 1–2 weeks later and again if needed
- Checks their understanding of the sick-day rules at subsequent visits
- Ensures paperwork has up to date information and contacts

Besides the time of diagnosis, another potentially critical time is transition, when the child moves to an adult clinic and parents may no longer attend the appointments. At this point it is vital to check the child's understanding of their condition, their medication and the sick-day rules, and to encourage them to wear a medic alert.

Paediatric Cushing's syndrome

Helen Storr (Barts and the London NHS Trust, UK) provided an overview of paediatric Cushing's syndrome, which is caused by overproduction of glucocorticoid steroids, resulting in weight gain, growth failure, osteoporosis, hypertension and virilisation.

It is divided into adrenocorticotrophic hormone (ACTH)-dependent Cushing's syndrome, which

is usually caused by cortisol-producing pituitary adenomas, and ACTH-independent forms. In the latter, ACTH levels are low and symptoms result from high levels of exogenous steroids or, rarely, adrenal tumours. Use of exogenous steroids is the most common cause of Cushing's syndrome in children of all ages.

Therefore, *healthcare providers should always question patients' families about steroid use, whether oral, parenteral, inhaled or topical.*

Endogenous Cushing's syndrome is very rare in paediatric patients. Adrenocortical tumours are the most common cause in preadolescent patients, with Cushing's disease (caused by pituitary adenomas) most frequent in older children. The symptoms usually appear gradually over several years. *It is therefore helpful to ask parents to bring older photographs of their child, to trace the evolution of the characteristic facial changes.*

A consequence of this gradual onset is that diagnosis is often delayed, leading to later problems including reduced adult height, low bone mineral density, arrested puberty, obesity and metabolic complications, fatty liver, and neuropsychiatric symptoms, including a poor performance at school.

What to look out for:

- Weight gain.
- Growth failure.
- Facial changes.
- Pre-puberty virilisation (generally advanced pubic hair).

Note that young patients may present only with weight gain.

The classic presentation is obesity along with a reduced height standard deviation score. In other words, *obesity plus growth failure is a red flag for Cushing's syndrome.*

The most straightforward test in children is 24-hour urinary free cortisol. This misses a

few cases, however, so patients with a negative test but high clinical suspicion of Cushing's disease should undergo a midnight (sleeping) cortisol test: cortisol should be undetectable at night. Testing cortisol at 09:00 misses many positive cases, but the low-dose dexamethasone suppression test (every 6 hours for 48 hours) is "reasonable", missing only a couple of cases.

Identifying the aetiology requires a 09:00 ACTH test to differentiate between independent and dependent forms, the latter pointing to the presence of a tumour.

Although magnetic resonance imaging can confirm a tumour, it is a poor predictor of its location, so Storr's team prefers to conduct bilateral inferior petrosal sinus sampling, in which corticotrophin-releasing hormone is given to stimulate ATCH production. This confirms that the ATCH production driving Cushing's disease is coming from the pituitary, and often the difference between the left and right sides gives a clue to location.

Treatment involves transsphenoidal surgery (through the bone at the back of the nose) to remove the tumour; experienced surgeons achieve the highest rates of remission – around three-quarters of patients. *Relapse is rare but does happen and can occur years after surgery, so children need to be followed up* and treated with radiotherapy or even bilateral adrenalectomy in extreme circumstances.

There is also a role for medical therapy, most commonly metyrapone etomidate, which is given for urgent cortisol reduction in patients with severe symptoms or as part of preparation for surgery or while waiting for radiotherapy to take effect.

Even children with remission often have persistent treatment needs, however, with long-term problems including pituitary hormone deficiencies and neuropsychiatric issues.

Height, weight and bone mineral density improve, but most patients need growth hormone treatment to offset earlier growth losses.

Why Martin Savage always measures plasma androgen in girls with virilisation

During the breakout sessions, Martin Savage (Barts and the London NHS Trust, UK) related a case of a 9-year-old girl with some pubic hair and mild acne. Although virilisation is the most common presenting feature of adrenal tumours, it occurs in only around 50% of cases of this already extremely rare disease, making premature adrenarche or late-presenting CAH the much more likely possibilities. Indeed, during 30 years of practice Savage has encountered only around 10 cases of children with adrenal tumours.

But he said that “somebody had their hand on my shoulder” that day and he opted to measure plasma androgen, leading to the identification and successful treatment of an adrenal tumour. “Ever since then, however benign or trivial the virilisation is that I’ve seen in a girl, I’ve always measured androgen,” he said. “Because I was lucky on that occasion.”

Savage’s talk focused specifically on tumours affecting the adrenal cortex (adrenocortical tumours). These are more common in girls than in boys, are most often seen in children younger than 5 years, and tend to occur in patients with genetic susceptibility, such as those with Li-Fraumeni syndrome or multiple endocrine neoplasia type 1 syndrome.

Presentation is very variable, because of the mixture of hormones secreted by the tumours. Most are malignant, but two-thirds can be removed, with complete resection resulting in an 80% survival rate. However, the prognosis for children who do not achieve complete resection is very poor.

Primary adrenal insufficiency

Steve Shalet (University of Manchester, UK) opened his presentation on primary adrenal insufficiency by stressing the importance of the subject, noting that *rather than primarily affecting quality of life, as is the case with most endocrine conditions, adrenal insufficiency is actually life-threatening.*

Autoimmunity accounts for around 90% of primary adrenal insufficiency, with other causes including haemorrhage, metastases,

infections and bilateral adrenalectomy, but in children CAH accounts for 80% of cases.

Other causes of primary adrenal insufficiency include the following:

- Adrenal hypoplasia congenita, caused by mutations in genes involved in adrenal development.
- ACTH insensitivity syndromes, caused by faults in the ACTH receptor.

- Other metabolic disorders including mitochondrial disease, the X-linked condition adrenoleukodystrophy, and Wolman's disease.

Certain medications can also cause adrenal insufficiency, including CTLA-4 inhibitors and drugs that accelerate cortisol metabolism, such as mitotane and ketoconazole. Interestingly, treatment with thyroxine can contribute to adrenal crisis in patients who have both thyroid and adrenal disease,

because excess thyroid hormone accelerates cortisol metabolism.

It is important to obtain a genetic diagnosis for primary adrenal insufficiency if at all possible, especially in familial cases, syndromic forms and young patients. This aids with determining the prognosis, starting appropriate treatment and avoiding unnecessary treatments, screening for concomitant disorders and offering genetic counselling.

Bullying and the paediatric endocrine patient

Bullying is common, affecting up to a third of children, particularly in the case of those with disabilities or chronic illness. It has multiple effects on self-esteem, sleep, mental health and academic performance, among others, which can last into adulthood.

Interviews with endocrine patients have uncovered missed opportunities to intervene, with patients saying that their healthcare providers rarely seemed to understand their problem or referred them to counselling services.

In the session on bullying, Andrew Dwyer (Centre Hospitalier Universitaire Vaudois, Switzerland and Boston College, Massachusetts, USA) outlined the PENS/ESPENS position statement on bullying, of which he is a co-author. It contains nine statements encompassing:

1. evidence-based practice to prevent, identify and respond to bullying;
2. coordinated efforts between healthcare professionals;

3. reducing stigma via the broad dissemination of psycho-educational programs;
4. empowerment-based programmes to help individuals, peer groups and communities manage bullying;
5. a call for national collection of data on bullying;
6. the need for more quality research into the impact of bullying;
7. collaboration within the medical profession and with other professions, such as education and juvenile justice;
8. legislative and regulatory action; and
9. access to affordable and appropriate mental health services.

Such aims, targeting the physical, mental, social and educational aspects of bullying, require an integrated, multisystem response from healthcare, families and peers, schools and policymakers. What is more, the response must be adapted to meet the changing needs of patients throughout their lifespan.

So how should nurses respond to the problem of bullying? The first thing is simply to ask: research suggests that exploring sensitive topics can give patients a more positive view of the clinic visit. But nurses do not need to feel as if they are prying; the subject can be approached in a neutral way, by discussing bullying in general before asking whether the child feels comfortable at their school and with their peers. Children's situations change, so it is worth making these enquiries at every clinic visit.

Nurses can support patients experiencing bullying in a variety of ways, most importantly by stressing that it's not their fault.

Patient beliefs and medication adherence

The presentation from John Weinman (King's College London, UK) on medication adherence delved not only into the beliefs of patients, but also of nurses. He demonstrated via an audience vote that *healthcare professionals err on the side of optimism, believing their patients to be more adherent than they probably are, and to be more adherent than average.*

The most likely rate of nonadherence is in fact 30–40%, and it can occur during any or all of the three phases of long-term medication use (initiation, implementation and persistence), with different reasons underlying the problem at different stages. Nonadherence is considered to be the largest threat to the efficacy of medication, resulting in a huge economic cost due to the additional healthcare resources used by nonadherent patients.

Nonadherence is traditionally divided into two categories: intentional and unintentional

Other things nurses can tell patients include:

- Ignore the bully – but not the bullying;
- Do not retaliate;
- Say: “Stop!” and walk away;
- Tell a parent or trusted teacher; and
- Stay near a trusted adult or larger group of peers.

Nurses can also be a resource for parents, communicate with the school, make referrals to other healthcare professionals who can help, follow-up with the child and advocate in the community

nonadherence. Intentional nonadherence is driven by patients' misunderstanding of their condition or treatment and/or by concerns about the treatment, whereas unintentional nonadherence is an effect of factors such as poor communication, poor planning and financial barriers. These categories are rather simplistic, however, given that drivers of intentional nonadherence, such as concerns about the treatment, can influence unintentional nonadherence, such as forgetfulness.

Current thinking on the drivers of nonadherence is summarised in the COM-B model, in which **C**apability, **O**pportunity (external social and physical factors) and **M**otivation combine and interact to produce adherence **B**ehaviour.

Nearly 100 factors including treatment adherence have been identified, but the strongest evidence to date is for:

- concerns about treatment;
- beliefs about illnesses;
- cost;
- perceived need for treatment; and
- perceived drug efficacy.

Patients' beliefs are critical because they are rarely disclosed during consultations, yet it is crucial for providers to be aware of them because beliefs are not set in stone and can be changed.

Key beliefs encompass patients' perceptions of their illness and of its treatment, as well as their ability to manage the treatment.

Of these, treatment beliefs are most closely associated with adherence or lack thereof, most specifically, a low conviction of the need for treatment coupled with high concern about its side-effects and/or long-term efficacy.

Healthcare providers should therefore use patient visits as an opportunity to discuss their beliefs and form strategies to mitigate any potential impact on adherence, as follows:

- Check patients' understanding.
- Provide a rationale for the necessity of treatment.
- Elicit and address concerns.
- Agree a practical plan to make medication a routine.
- Identify possible barriers.

Spotlight: are growth charts an accurate reflection of treatment adherence?

During a case presentation, Wendy Schwartz (Alberta Children's Hospital, Calgary, Canada) showed data where she had the opportunity to compare adherence to growth hormone treatment as implied by patients' growth charts with the reality, ascertained using data from the Easypod injection device. She found that, on a visit-by-visit basis, growth velocity does not always match up with medication adherence, so nurses cannot assume that a spell of poor growth always reflects poor adherence and, conversely, that a good short-term response signifies perfect medication adherence.

Growth disorders: key messages and update

Rounding off the symposium, Martin Savage (Barts and the London NHS Trust, UK) recapped key points on the management of growth disorders, covered in detail in previous *IMAGE meetings*.

Recombinant human growth hormone (rhGH) is licenced for use in many conditions, but the exact ones vary between countries; for example, it can be used to treat skeletal

dysplasias in Japan. The conditions are all very different from each other, and the patients produce varying levels of endogenous GH, affecting their responsiveness to rhGH and therefore the required dose. For example, a child born small for gestational age will need a higher dose to achieve the same response that a child with isolated GH deficiency would achieve.

This underlines the need for individualised therapy, with dose based on the factors that predict growth response in that particular child. Although predictive models do exist, they are too complicated and time-consuming to have gained much traction in the clinic. However, it is helpful to know the factors on which the models are based.

- The diagnosis
- Patient age
- Presence and severity of GH deficiency
- Parental heights
- rhGH dose
- Growth response during the first year of treatment

The importance of these factors varies according to the condition; for example, the severity of GH deficiency is the top predictor of treatment response in GH-deficient children, where rhGH dose is the top predictor for patients with Turner syndrome and those born small for gestational age. Added to that, is that patients vary as to how important stature is to them, further necessitating an individualised approach.

The efficacy of rhGH can be given a boost by adjuvant treatments, specifically aromatase inhibitors and gonadotropin-releasing hormone analogues. These work to increase the window of opportunity for rhGH treatment, the former by slowing bone age progression and the latter by delaying puberty. Both treatments require pre-planning, rather than being added at the last minute as a “desperate measure”, because they need to be given for at least 2 years, and ideally 3 or 4 years.

A more recent development is the advent of long-acting rhGH, which Savage believes will come onto the market in around 3 to 4 years’ time. Several such formulations are in clinical development, using pegylation, prodrug formulations and fusion proteins to slow the release of the medication.

This allows treatment to be given just once weekly, with theoretical benefits for treatment adherence and quality of life, resulting, ultimately, in improved final height. But will it? John Weinman pointed that, for the majority of patients, access to a once-weekly formulation does not actually address the primary reasons for nonadherence.

