

Insights into **MA**naging **G**rowth for **E**ndocrine **N**urses

10-11 October 2019, Bordeaux, France

An Independent Medical Education event for Paediatric Nurses



Meeting Report



IMAGE 2019: INSIGHTS INTO MANAGING GROWTH FOR ENDOCRINE NURSES

And so concludes our 5th annual IMAGE meeting, this year inhabiting the beautiful city of Bordeaux, France. For this meeting we turned out attention to the nurse's role in the management of disorders of appetite, late endocrine effects of childhood cancer treatment, family interaction related to chronic disease and clinical and diagnostic reasoning related to growth and puberty.

The sessions were varied in content and format, including engaging presentations, case studies, and a practical coaching workshop.

We hope you enjoyed the meeting and it helps support you in your daily clinical practice. This summary reports the highlights from across the 2 days.

APPETITE CONTROL

WHAT CONTROLS APPETITE?

Tony Goldstone (Imperial College London, UK) kicked off the meeting looking into what factors control appetite. The concept of appetite is becoming increasingly complex as we discover more about the mechanisms behind it.

storm of biology which predisposes the body to obesity”.

The regulation of food intake involves a complex interaction of systems that determine the size, content and frequency of “feedings”, with the brain processing both the central and peripheral signals. The hypothalamus is central to this, with associated

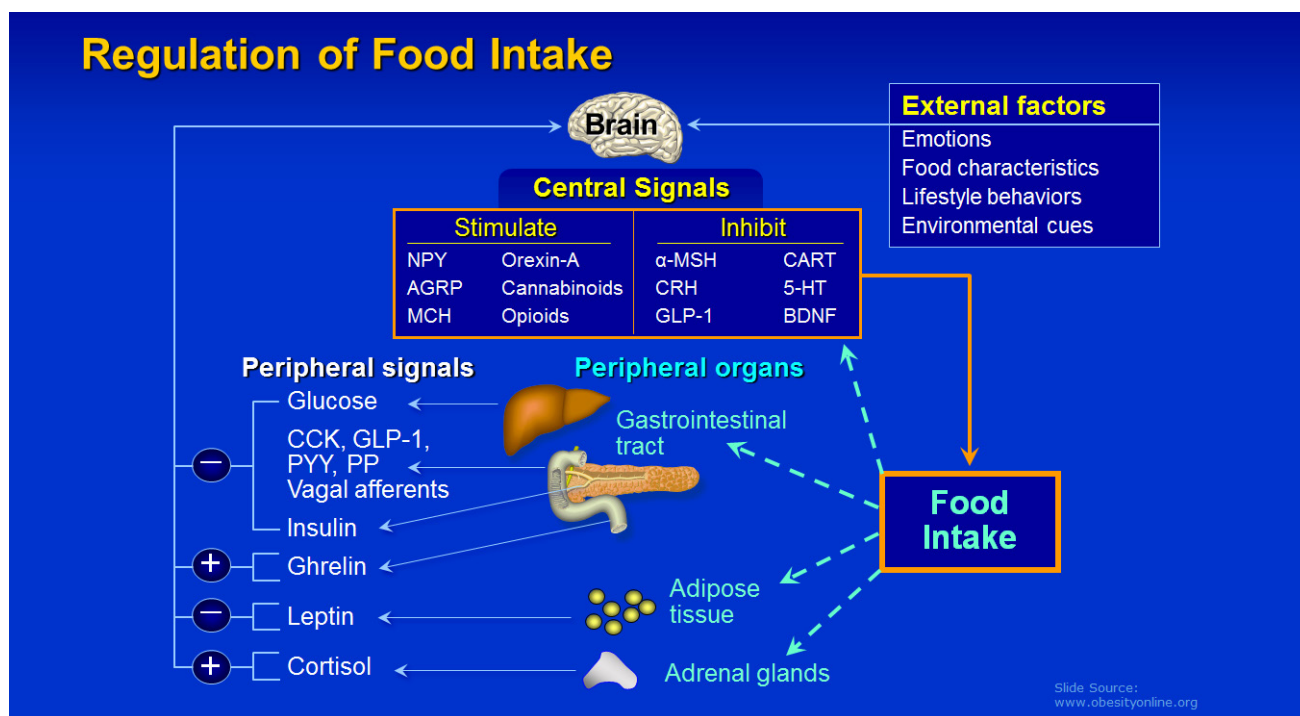


Figure 1: Regulation of food intake

There are several behavioural factors known to be involved in over-eating such as increased hunger or reduced satiety, emotional or stress-induced eating, and impaired ability to reduce overeating or “will-power”. Behind each behavioural factor there are physiological mechanisms, which are important to understand in order to manage this often stigmatised condition, which Goldstone described as the “perfect

neuronal circuits identified that affect both satiation (the level of fullness) and satiety (the level of hunger). The discovery of leptin in 1994^[1] was a turning point in the understanding of appetite, which Goldstone explained “turned obesity, for the first time, into a disease which had a scientific underpinning”. Leptin is produced by adipose tissue and binds to a receptor in the hypothalamus, which stimulates the release



of neuropeptides and transmitters that inhibit food intake. One of the known causes and effects of obesity is leptin resistance. The levels of leptin also decrease with prolonged fasting, in both obese and lean people, indicating one of the reasons it is hard to maintain weight loss. There are several other peripheral hormones known to have a similar effect to leptin but with more short-term effects, such as glucose and insulin as well as oxyntomodulin, PYY and glucagon-like peptide (GLP)-1. Some of these are now being used as therapeutic targets, such as GLP-1 agonists, which have been shown to produce weight loss in non-diabetic obese patients.

Ghrelin has the opposite effect in that it increases when fasting and decreases when food is consumed, thus stimulating appetite. Perhaps surprisingly, studies have reported that the ghrelin level is in fact reduced in obese patients; however, it then increases when weight loss occurs representing another barrier to maintaining long-term weight loss ^[2].

These hormones all act on the hypothalamus through different pathways and prompting different neurochemical responses. Within the hypothalamic nuclei there are both orexigenic and anorexigenic neuropeptides which, Goldstone explained, creates a “ying yang” system with the same hormone inhibiting one neuron while stimulating another. The improved understanding of these different hormones and mechanisms has led to the development of targeted drugs (such as phentermine, topiramate and bupropion), which give hope for the pharmacological management of obesity.

To complicate matters further, food intake also affects several other neuronal circuits such as the orbitofrontal cortex, which is associated with reward value, and the nucleus accumbens, which is associated with addiction. Obesity has been shown to cause a decrease in responsivity to food consumption but an increase in anticipatory and consummatory reward response to food.

The only treatment known to result in long-term weight loss is surgery, with gastric bypass achieving up to a 25% weight loss sustained for up to 15 years post-surgery ^[3]. Gastric bypass has also demonstrated efficacy in adolescent patients for both weight change and remission of type 2 diabetes and hypertension; therefore, it is likely to be increasingly used in younger patients.

Goldstone concluded that “if we want to find treatments, whether it be drugs or bariatric interventions, we need to try and understand the circuitry and pathways to target for weight loss”.

MANAGEMENT AND PROGNOSIS OF CHILDHOOD OBESITY

The management of childhood obesity is an issue that requires more work. As Antje Körner (University Hospital for Children and Adolescents, Leipzig, Germany) stressed: “We are not quite there yet”. To tackle the condition, it is important to understand all factors contributing to obesity.

A recent longitudinal study clarified the onset age for common obesity, demonstrating that it can manifest in children as young as 2 years old, with a critical age range for development of sustained obesity of 2–6 years ^[4].

There are several risk factors proven to influence development of childhood obesity, such as ^[5]:

- parental weight;
- low socioeconomic status;
- weight gain in pregnancy (>21 kg); and
- high birth weight (>4000 g).

Körner highlighted that the risk is contributed to by both lifestyle and genetic factors. Several genes have been identified as predictors of obesity, such as *TMEM18* and *FTO*. However the effect of each single nucleotide polymorphism in isolation is small.

As is widely known, common obesity is becoming increasingly prevalent; however, monogenic obesity is rare, occurring in less than 5% of the population. Körner explained that to identify monogenic obesity, a thorough clinical examination and history must be undertaken as well as the development of a detailed growth chart. Indications for monogenic or syndromic obesity include:

- early-onset obesity;
- extreme obesity (BMI > +4 SDs);
- normal weight in the parents or other family members;
- consanguineous parents;
- hyperphagia; and
- short stature.



Genes linked to monogenic obesity are different to that of common obesity with the most frequent defect being in the *MC4R* gene. Other associated genes include leptin (*LEP*), leptin receptor (*LEPR*), *POMC* and prohormone convertase 1/2 (*PCSK1*), variants in which may result in a variety of clinical characteristics.

Obesity in childhood can have a huge impact on adult life. The rates of premature death in adults who were obese in childhood were significantly increased in a cohort study of approximately 5000 American Indian children followed up for over 20 years. In addition, childhood obesity is linked to preclinical metabolic and cardiovascular failure, and may also lead to young-onset diabetes, which is a “more lethal phenotype of diabetes” when compared with type 1 diabetes [6].

To identify impaired glucose metabolism, the American Diabetes Association (ADA) currently recommends measuring the following:

1. Two-hour plasma glucose from an oral glucose tolerance test (OGTT).
2. Fasting glucose and/or insulin.
3. Glycated haemoglobin (HbA1c) levels.

However, Körner cautioned that these criteria do “not entirely reflect the progressing hyperinsulinaemia and insulin resistance in obese children” and that the “reproducibility of OGTT (blood glucose) results is poor”. It is therefore important to look out for other indicators of potential prediabetes such as acanthosis nigricans.

Körner concluded by stressing that “obesity is NOT the fault of the children”. Treatment is not yet very successful; therefore, more research needs to be done into the mechanisms and more pre-emptive and individualised strategies need to be developed.

CLINICAL ABNORMALITIES OF APPETITE CONTROL

Tony Goldstone’s second presentation of the morning looked further into genetic obesity. He began by highlighting how challenging it is to manage these conditions due to the multi-organ effects and thus the need for a multi-system management approach.

The most common monogenic cause of obesity is the *MC4R* mutation which is present in approximately 5% of monogenic obesity cases [7]. Goldstone explained that understanding the genetics can create potential for revolutionary treatments that target the mutations and pathway disruptions. He used the example of setmelanotide targeting the *MC4R* signalling pathway, which has promising results although it “doesn’t solve everything” [8].

Prader-Willi syndrome (PWS) is the most common syndromic cause of obesity with an incidence of one in 30,000 births. Primary symptoms include morbid hyperphagia and obesity. Interestingly, they tend to manifest around the same time as “common” obesity (2–5 years of age); therefore, healthcare professionals need to be alert to more specific PWS symptoms.

The major criteria for identifying PWS are [9]:

- Neonatal hypotonia.
- Feeding problems in infancy.
- Excessive childhood weight gain.
- Facial features.
- Hypogonadism.
- Developmental delay.
- Hyperphagia.
- Chromosome 15q11–13 abnormality.

The severity of the symptoms can be highly variable with research showing that children diagnosed later typically experienced more severe hyperphagia [10]. This variability is not yet fully understood.

The genetics is also complicated, with several possible mutations to the chromosome 15q11–13 resulting in PWS, and more still likely to be discovered. Understanding them is crucial nonetheless in order to inform treatment research. Many of the mutations are understood to be present on the SNORD116 and SNORD115 cluster and cause a number of downstream effects in the hypothalamus [11].

In contrast to obese patients, PWS patients have elevated post-prandial ghrelin levels. There are also a number of other peripheral abnormalities such as impaired pancreatic polypeptide secretion highlighting how widespread the condition is, affecting many areas of the body.



PWS has a gradual and complex progression, which can make it difficult to diagnose early as, for the first few years of life, PWS children can follow the normal centiles. In light of this, Goldstone explained how, alongside several colleagues, he helped develop a more detailed set of nutritional phases to help clinicians to identify the condition ^[12].

Nutritional Phases

- 1a) Hypotonia with difficulty feeding (0-6 mos.)
- may also have FTT despite adequate calories
- 1b) No difficulty feeding, growing on curve (3-24 mos.)
- 2a) Weight ↑ without ↑ in calories (1.5-3 yrs.)
- 2b) Weight ↑ with ↑ in calories (2-12 yrs.)
- 3) Hyperphagic, reduced satiety (3-21 + yrs.)
- 4) Prev. 3), but appetite is less now (adulthood)

Miller JL et al. Am J Med Genet 155A:1040-9, 2011

Figure 2: Prader-Willi syndrome nutritional phases

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The most common causes of death in PWS patients are obesity related, particularly pulmonary complications; however, there have been other unique causes described such as gastric rupture and choking.

As the understanding of the condition has improved, earlier diagnosis has become more achievable with the average age of diagnosis now in the first few weeks or months of a child's life. Goldstone described the importance of the multidisciplinary team (MDT) to work together to ensure correct diagnosis and management as well as to educate the family early on. The condition demands involvement of many different specialties from gastroenterologists to sleep disorder specialists.

Once the diagnosis has been made, "GH [growth hormone] therapy should be started early in childhood, taking into account caution and relative contraindications". The benefits of GH treatment go beyond just increasing final height, as it can also improve body composition, strength and endurance and respiratory quotient, as well as improving the patient's sense of wellbeing. Goldstone cautioned against the use of GH in patients who are very obese, however. Whether GH should be carried into

adulthood or not remains a complex decision and varies country-to-country.

Goldstone highlighted his key recommendations for the management of PWS:

1. Vigorous control of the food environment and regular exercise is essential to manage hyperphagia and obesity.
2. Management of transition from adolescence to adulthood requires specific attention and care, particularly with regard to patient autonomy and endocrine issues.
3. Increased availability of group homes with experience in the management of PWS is needed to help placement, quality of life, and health issues in adulthood.
4. Recognition of the distinction between the underlying behavioural problems seen in PWS and acute psychiatric illness is essential.

Goldstone also underlined the success of specialist residential group homes in the UK and advised delegates to endorse their use in their own countries where possible.

To manage obesity associated with PWS, consistency is important in order to reduce the anxiety around food. Similarly to the initiation of GH, early establishment of a low-calorie, well-balanced diet is key, alongside appropriate psychological and behavioural counselling of the patient and family.

Pharmacological treatment has not been greatly successful to date, although several ongoing trials are providing some interest and promise, for example GLP-1RAs and oxytocin.

Goldstone summarised by further stressing the importance of early diagnosis and MDT management and that the role of the endocrine nurse within this MDT is critical for many reasons, one being so the patient feels there is some consistency in their clinical management.

OBESITY IN PRACTICE

PRADER-WILLI SYNDROME – Christelle Tressens (Hôpital des Enfants, Toulouse, France)

A male infant was transferred to a neonatal department with hypotonia, feeding difficulties, and weak and uncoordinated sucking. Other observations included a triangular mouth, weak cry and cryptorchidism.

Genetic testing showed an imprinting defect on chromosome 15, which led to the diagnosis of PWS on day 20 of life.

Tressens again stressed the importance of MDT working due to the complex symptomatology and progressive phases of PWS. Citing the PWS nutritional phases (see figure 2), she stressed the importance of closely monitoring BMI in phase 2a.

To effectively manage PWS, Tressens advised delegates:

- to not only focus on the food aspect of the syndrome but also to consider the outside interests of the child to help manage the condition;
- that early diagnosis is crucial; and
- to ensure coordination between all the different disciplines involved.

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COACHING FOR OPTIMAL FAMILY INTERACTION

Katie Frost (KT Training and Coaching Ltd, UK) began by stating that “despite logical and rationale ways forward, these are often blocked by emotional and behavioural barriers”. A large part of managing paediatric disorders is addressing the psychological and emotional issues of both the child and the parents or family, which is where motivational interviewing can provide support.

“Motivational interviewing is a collaborative conversation style for strengthening a person’s own motivation and commitment to change” ^[13], she explained, which relies upon compassion, acceptance, collaboration and evocation.

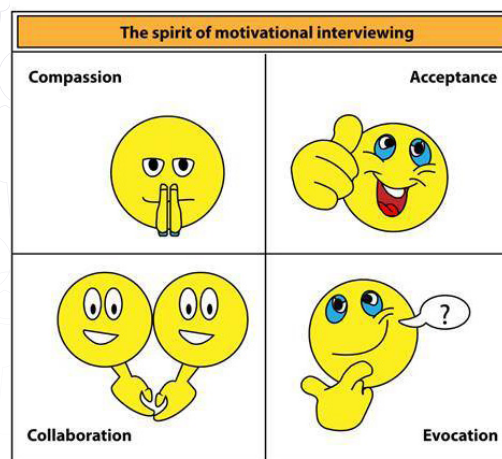


Figure 3: The spirit of motivational interviewing

It is important to avoid judgemental behaviours and recognise that you are “not the only expert in the room”, as the patient and family are the ones living with the condition.

Following a breakout session in which nurses discussed the difficulties and successes during conversations in their own clinical practice, Frost described two mnemonics, “OARS” and “RULE”, which can act as a reminder of the principles and core skills required in motivational interviewing:

OARS

- **Open** questions, such as “What are your hopes for your consultation today?”, “I’m curious to learn how you have been getting on with decreasing your child’s intake of snacks”, or “Help me understand more about why you would even consider modifying your diet”.
- **Affirmations**, such as “I can see it took courage for you to talk about this” and “your creative ideas around increasing physical activity are very helpful”.
- **Reflective listening**, such as “this sounds important for you to overcome” and “I’m wondering if you are finding it difficult to know where to begin with this”
- **Summaries**, such as “let me see if I have this right” and “so what you are saying is...”.

RULE

- **Resist** the urge to “fix things” and tell them what to do.
- **Understand** others’ motivation, including their values, needs and barriers.

- Listen with empathy.
- Empower others to set their goals, put plans in place and find ways to overcome any obstacles.

Delegates were then able to practice these techniques in one-to-one role plays and reflect on how they changed the dynamics of the conversation.

Frost finished by saying that “we can work with motivational interviewing to evoke others’ motivation to change”.

OBESITY IN PRACTICE

CUSHING’S DISEASE – Judith van Eck (Sophia’s Children’s Hospital, the Netherlands)

A 14.5-year-old girl was referred by her paediatrician because of growth retardation despite puberty and weight gain. Her mother was known to have hyperparathyroidism. Physical examination demonstrated a full moon face and hirsutism. Her height and weight charts showed a sudden increase in her BMI alongside the halt in height velocity, known as the “endocrine cross” in the Netherlands, van Eck explained.

Biochemical tests showed a very low serum cortisol level at around midnight, which is one of the key signs for Cushing’s syndrome. Magnetic resonance imaging of the patient’s pituitary indicated a micro adenoma and consequently she was diagnosed with adrenocorticotrophic hormone-dependent hypercortisolism, or Cushing’s disease. Due to the mother’s hyperparathyroidism diagnosis, genetic testing was carried out, which led to the discovery that she also had MEN-1 syndrome, a very rare disorder causing tumours in the endocrine glands.

Following curative surgery the girl developed secondary adrenal insufficiency, which was treated with hydrocortisone substitution, leading to the recovery of the hypothalamic–pituitary–adrenal axis.

Judith highlighted the need for nurses managing Cushing’s disease to have the specialist skills and knowledge to be able to manage this rare syndrome.

THE ROLE OF THE PAEDIATRIC ENDOCRINE NURSE SPECIALIST

THE EXPANDING ROLE OF THE PAEDIATRIC ENDOCRINE NURSE SPECIALIST

Edouard Thomas (Centre Hospitalier Universitaire de Toulouse, France) opened by summarising the history of the Advanced Practice Nurses (APN), which originated in the USA in the first half of the 20th century, with the UK, Canada, Holland, Australia and Brazil following suit a few decades later.

The development of APN can provide many benefits to global healthcare systems, for example:

1. Improve access to care in a time of physician shortages as well as to underserved populations.
2. Reduce healthcare costs.
3. Provide a solution to the changing demand for different forms of care. For example, due to the ageing population, there is an increasing demand for home-based and nursing home care options.
4. Drive nurse recruitment and retention by providing improved career prospects.

Despite the clear benefit of driving their development, “the number of APN still represents a small proportion of all nurses”. Thomas commented that this is primarily due to the lack of global consensus on the definition and role of APN. This in turn is perhaps because countries are at different implementation stages of these advanced roles; for example, in France, there are only pilot projects in primary care and chronic disease management, not across all disciplines. As such the competencies and practices within diagnosis and treatment that the APN is involved in varies from country to country. Finally, the educational requirement to become an APN also varies, with some countries requiring a Master’s degree while others have only recently introduced these courses for nurses.

Specifically within paediatric endocrinology, the roles of the APN include, but are not limited to: direct clinical practice, education, consultation, research, care coordination and transition to adult care, and independent prescribing. Due to their role in the day-to-day education and follow-up, they are critical in maintaining some level of clinical continuity in the management of complex endocrine conditions.

'MY ROLE' IN FRANCE, CANADA, FINLAND AND THE NETHERLANDS

To highlight the first-hand experience of specialist nurses from across the world, Christelle Tressens, Wendy Schwarz (Alberta Children's Hospital Calgary, Canada), Anne-Karin Ramstad (Helsinki University Hospital, Finland) and Judith van Eck each spoke about what their role entails in their separate countries.

The presentations highlighted both the similarities and differences between the roles in each country. Schwarz explained that, in Canada, they have nurse-run clinics alternated with physician visits, which help to reduce waiting times. They coordinate and perform all endocrine testing, provide education to the patient and family, and are involved with prescription renewals on direction from the physician. They also have the opportunity to be involved in research both at the international and local level.

Conversely, Ramstad explained that nurses in her centre do not do any testing; however, they are involved in device education and treatment administration. van Eck explained how, in order to establish clinical nurse specialists in the Netherlands, they took inspiration from Canada, using the CanMEDS competency framework^[14] to develop the role. They thus have a similar level of responsibility as Canadian nurses, carrying out most endocrine tests and follow-up with growth hormone and obesity treatment as well as providing critical education.

In France, Tressens explained, the role of the specialist nurse tends to be limited to recommending the devices and they do not regularly provide medical advice. Nonetheless, throughout the treatment of a child with GH they will be involved at several stages, including choosing the injection device and starting the GH treatment. They now also provide the follow-up appointments during the first year, which used to just be the responsibility of the physician.

All four country representatives highlighted a need for more progress and more responsibility to be given to nurse specialists and, with the importance of their roles becoming more and more evident, this is something all healthcare systems should be working towards.

OBESITY IN PRACTICE

POLYCYSTIC OVARY SYNDROME – Kate Davies (London Southbank University, UK)

A 13-year-old girl was referred to paediatric endocrinology due to a high BMI and unexplained weight gain. She had been experiencing heavy but regular periods for which she was prescribed the contraceptive pill, which led to some improvement.

A pelvic ultrasound showed multiple microcysts with an appearance suggestive of polycystic ovaries. The mother wanted no further endocrine follow-up; therefore she was referred back to primary care for a dietician referral; however, this referral was never made.

A few months later she presented to gynaecology with amenorrhoea and abdominal pain. She was prescribed folic acid/myo-inositol sachets, which helped with menstrual cycle disturbances, obesity and hyperandrogenism. The girl was also referred to dermatology due to increased hirsutism and acanthosis nigricans. Davies explained that the latter is a "visible marker which strongly suggests insulin resistance".

The following year she was referred again to paediatric endocrinology where an OGTT test showed high androstenedione levels and low sex hormone binding globulin (SHBG), which Davies explained is classical of polycystic ovary syndrome (PCOS).

PCOS affects 8–13% of all women, Davies concluded, with a genetic link thought to be the primary cause. She stressed the importance of MDT working due to the complex nature of the condition and that parents should receive more education and support to help support their child as the psychological impact can be significant.

LATE ENDOCRINE EFFECTS OF CANCER THERAPY

The impact of cancer treatment on the endocrine system is becoming a "new epidemic", said Stephen Shalet (Christie Hospital and the University of Manchester, UK), referencing that approximately



44% of cancer survivors develop at least one endocrinopathy later in life.

There is a wide ranging group of endocrinopathies that can be induced by cancer treatment, which include:

- Hypopituitarism.
- Obesity.
- Thyroid dysfunction.
- Thyroid tumours.
- Hyperparathyroidism.
- Infertility.
- Hypogonadism.
- Osteoporosis.
- Metabolic syndrome.
- Insulin resistance.
- Diabetes mellitus.

Radiation-induced hypopituitarism

Children who have received treatment with prophylactic cranial irradiation or total body irradiation are at risk of radiation-induced hypopituitarism, and also thyroid damage. The effect is dose and time dependent with higher doses of radiation producing a larger and faster effect ^[15].

The younger the age the child is at irradiation, the earlier they will go through puberty which is likely to lead to short stature. Shalet commented that this may be difficult to spot in male children, however, as the radiation may affect the development of the testes, which is the first sign of puberty.

He also highlighted the importance of the timing of treatment initiation. Initially clinicians were cautious about starting GH due to a lack of safety data; however, research now shows that around 50% of patients would be GH deficient by 1 year post-treatment and that the previous standard of waiting at least 2 years should be left behind. Moreover, there is currently no evidence that GH increases the risk of primary tumour recurrence.

Hyperinsulinemia, impaired glucose tolerance and diabetes mellitus

Hyperinsulinemia and its associated metabolic abnormalities have been reported in approximately 18% of long-term survivors of childhood cancer ^[16], particularly if the child has received a bone marrow transplant.

A prospective study found that the risk of obesity is not increased, however “prevalence of abdominal adiposity in prepubertal and pubertal subjects was roughly doubled” alongside an increase in fasting insulin concentration.

The independent risk factors for developing these conditions included ^[16, 17]:

- total body irradiation;
- untreated hypogonadism;
- abdominal adiposity; and
- radiation dose >10 Gy.

Reproductive endocrinology

Shalet went on to describe the reproductive and fertility issues that can be caused by childhood cancer treatment, mentioning that the risk can vary dependent on gender and the chemotherapy agent used.

Ovarian function has been shown to be altered by allogeneic hematopoietic stem cell transplantation. The risk factors include:

- Older age at transplantation.
- Conditioning with total body irradiation.
- Leukaemia diagnosis.

An emerging area of research and interest is fertility preservation, with an increasing number of society guidelines recommending consideration of ovarian tissue cryopreservation and orthotopic reimplantation.

Shalet mentioned the emergence of the “new world” proton therapy also has the potential to reduce the collateral damage to healthy tissue to avoid the later endocrine effects.

To close, Shalet highlighted the St Jude lifetime study ^[18], which revealed that almost half of the childhood cancer survivors enrolled had severe growth hormone deficiency into adulthood with only one in 348 receiving growth hormone treatment. This “nontreatment” was shown to lead to additional poor health outcomes such as reduced muscle mass, energy expenditure and exercise tolerance. Shalet concluded that this is a “very damning observation of what happens to these individuals later in life” and indicates the need for these patients to be “monitored centrally”.



When asked about when a patient should be referred to the endocrine late effects team, Shalet advised that 1 year post-treatment would be his recommendation as doctors need to be sensitive to the fact that the child and family have just been through a gruelling cancer treatment regimen.

OBESITY IN PRACTICE

SHORT STATURE WITH OBESITY – Lee Martin (Barts Health NHS Trust, London, UK)

A 9.5-year-old boy presented with unexplained weight gain. He had a normal birthweight and was described being very sporty and having a healthy diet, although his parents felt his growth had slowed. A bone age X-ray uncovered a year's delay in bone age.

Martin explained that initial investigations looked at Cushing's disease, but this was ruled out due to normal urinary free cortisol and cortisol circadian rhythm. Subsequently, an IGF-1 test was carried

out to determine the levels of GH production, which was a little low. Therefore a GH stimulation test and insulin tolerance test were carried out, which led to the diagnosis of GH deficiency.

Obesity associated with short stature in childhood should be a marker for concern, Martin stressed. It can be complex to diagnose as childhood obesity is linked to reduced spontaneous GH secretion; therefore, he questioned whether there is a need for different GH cutoffs for children with higher BMIs.

In the final session, Lee Martin and Wendy Schwarz discussed interactive cases exploring a case of abnormal puberty and a complex endocrine case. And, to close the meeting, Martin Savage (Barts and the London School of Medicine & Dentistry, UK) presented a light-hearted quiz testing what the delegates had learnt over the course of the meeting intertwined with a few fun facts about the host city.

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