Thyroid disease in children

Special issue P5–9

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ESPE Liverpool – rescheduled to 7–9 May 2021 – see page 3
Of necessity, this issue of your newsletter begins by outlining the changes in plan regarding all ESPE’s activities for the remainder of this year. As you will be aware, the situation is evolving rapidly, and further information will be sent out to members from the ESPE Team as details are confirmed. The most notable change, as we publish, is the rescheduling of the ESPE Liverpool Meeting to 7−9 May 2021, from its original September 2020 date. Details about this and other activities are included on page 3.

The theme of this issue is ‘Thyroid disease’, and we thank our authors who have all written for us, despite the disruption they, like everyone else, have faced recently.

On page 5, Michael Zimmermann considers the assessment, impact and best methods for eliminating iodine deficiency. This preventable condition is a global risk factor for impaired child development, with an urgent need for intervention.

Paolo Beck-Peccoz looks at the challenges encountered in clinical management of central hypothyroidism on page 6. This disease can present a very variable clinical and biochemical picture, associated with mild to severe hypothyroidism.

Evidence from adult endocrinology suggests the presence of ‘resistance’ to exogenous thyroid hormone in 5−10% of the hypothyroid population. On page 7, José Moreno updates us on the latest understanding, and considers its relevance to paediatric patients.

Lastly, on page 8, Andrew Bauer examines the latest approaches in diagnosis and management of thyroid nodules and differentiated thyroid cancer in childhood, including the importance of oncogenic profile testing.

It remains for me to wish you well, as we continue to deal with unprecedented demands in our professional and personal lives. May you, your families, colleagues and friends enjoy good health in the coming months.

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Cover image: Garoshka/Stock

RESOURCES

ESPE Annual Review 2019
The Annual Review is an easily digestible round-up and celebration of everything ESPE achieved and was involved in last year. You might spot yourself or a colleague in there!

Please let us know how an ESPE activity has had a positive impact on your career, research, or the care you deliver to your patients. It’s always great to hear how the Society is making a difference, and we can reflect this in future reviews of our activities.

See www.eurospe.org/about/annual-review

ESPE e-Learning
Supporting this issue’s theme:

- ‘Management of children with acquired thyroid disease’ and ‘Neonatal thyroidology’ are chapters within Thyroid Disorders, in General Content. Six problem-solving cases are described in newborns, children and adolescents.

- ‘Thyroid disorders in resource limited settings’ is a chapter within Thyroid under Resource Limited Countries, where you will also find three problem-solving cases, all in five languages (English, French, Spanish, Chinese and Swahili).

IN ADDITION:

- Problem-solving cases have been added to the Diabetes ISPAD Guidelines in General Content.

- A case of a boy with type 2 diabetes mellitus has been added to the section Obesity.

www.espe-elearning.org (registration is free)

IN MEMORIAM

Otfried Butenandt remembered
It was with great sadness that we heard of the death of Professor Otfried Butenandt (Germany). Professor Butenandt had been an active ESPE member and a great mentor to many paediatric endocrinologists over the years. Our thoughts and sympathy are with his family, friends and colleagues at this very difficult time.

For a full obituary see www.eurospe.org/news/item/14086/Obituary-Prof-Otfried-Butenandt

EDITORIAL

Welcome

Since our last issue, the world has been transformed by the impact of the coronavirus pandemic. We have all been coping with challenges that we could never have anticipated. Many of these have been particular to those of us working on the front line of clinical care or providing crucial support. ESPE’s pride in its members and their work has never been greater than it is now.

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IN MEMORIAM

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COVID-19 and ESPE
The whole world has, of course, been reeling from the impacts of this year’s pandemic. We know that medical and scientific professionals globally have been facing unprecedented challenges. Our thoughts have been with you all.
Back in March, we produced a statement regarding COVID-19, offering guidance for members, parents and patients.


ESPE Liverpool rescheduled 7–9 May 2021
The decision to postpone our Annual Meeting in Liverpool from September 2020 into 2021 was hard. Thanks for your patience while we rescheduled this sizeable event. The revised dates are Friday 7 to Sunday 9 May, and not our usual Thursday to Saturday format. However, we are very fortunate to have secured the Liverpool venue so close to our planned May 2021 meeting dates. The ESPE Meeting that would have taken place in Copenhagen in May 2021 will now be moved to a future year.
Please watch out for the latest information via the ESPE website, social media channels and emails, including details regarding registration and abstract submission. We thank everyone involved in the work that has been necessary to achieve this.

You can find answers to FAQs at www.eurospe.org/meetings/2020/espe2020/postponement-faqs

Other changes
- ESPE Schools will not go ahead in 2020. Applications/accepted students will be rolled over to next year.
- ESPE Summer and Diabetes, Obesity and Metabolism Schools will take place on 4–6 and 10–12 May 2021, respectively, alongside the postponed ESPE Liverpool Meeting.
- Dates for other ESPE Schools will be set and publicised on the ESPE website in due course.
- The Science Symposium on congenital adrenal hyperplasia scheduled for October in Nijmegen, The Netherlands, has been postponed until 29–30 October 2021.
- The call for hosts for the 2021 Science Symposium has been withdrawn and a call will open for 2022 hosts next year.
- The Undergraduate Achievement Award deadline will be extended to align with the new abstract deadline for the postponed ESPE Liverpool Meeting.
- Other grant deadlines have remained in place, but with flexibility and the likelihood of longer than usual review times and project start dates.
- The Clinical Fellowship deadline has been extended from 31 May to 30 September.

Rare Disease Visiting Professorship
We congratulate the two successful applicants for this new ESPE grant.

Hedi Claahsen’s project is ‘Long term follow up and monitoring of treated and untreated patients with congenital adrenal hyperplasia: bridging the gap between developed and developing countries’. This is a collaboration between Augustini Utari at Diponegoro University, Indonesia, and herself in Radboudumc, The Netherlands.

Kenneth McElreavey’s study is entitled ‘Understanding the causes of disorders/differences of sex development (DSD)’. He and colleagues have recently identified genetic variants in a factor termed DHX37; they aim to understand why these mutations cause DSD. Collaborations with centres in North Africa and India have identified individuals carrying the variants.

Find out more about the Visiting Professorship at www.eurospe.org/grants-awards/grants/visiting-professorship
HOT TOPICS

Bringing you recent highlights from the world of research

Genetic analysis of testosterone’s role in disease

A new study by the MRC Epidemiology Unit (Cambridge, UK) has demonstrated that levels of testosterone are causally related to the risk of several diseases. Author John Perry commented that “Due to the growing interest in the use of testosterone supplementation, we thought it was important to begin to understand the full impact testosterone might have on disease risk.”

The researchers used a dataset of more than 425,000 women and men of European ancestry from the UK Biobank study. Testosterone’s causal role in disease development was notably different between men and women. High serum levels of testosterone were detrimental in women, increasing the risk of hormone-sensitive cancers, such as breast and endometrial cancers, and metabolic disorders, such as polycystic ovary syndrome and type 2 diabetes mellitus. In contrast, high levels of testosterone were largely beneficial in men, reducing the risk of type 2 diabetes mellitus and improving other aspects of metabolic health (such as fasting levels of glucose and body fat levels) but increasing the risk of prostate cancer.

Read the full article at Ruth et al. 2020 Nature Medicine 26 252–258, with a commentary at Greenhill 2020 Nature Reviews in Endocrinology 16 195

Liraglutide for adolescents with obesity

A randomised double-blind placebo-controlled multinational phase 3 trial to assess the efficacy of liraglutide (a glucagon-like peptide-1 analogue) in weight management was conducted at 32 sites in five countries. It included adolescents from 12 up to 18 years of age who were obese and had shown a poor response to lifestyle therapy alone.

The trial consisted of a 56-week treatment period and a 26-week follow-up period. Subjects were randomly assigned to receive either liraglutide (3.0 mg) or placebo subcutaneously once daily, in addition to lifestyle therapy. Liraglutide was found to be superior to placebo at week 56 with regard to the change in body mass index standard deviation score from the baseline (estimated difference −0.22; 95% CI, −0.37 to −0.08; P=0.002). The most common side-effect noted in the liraglutide group was gastrointestinal (occurring in 13 participants, compared with none in the placebo group). Thus liraglutide, with lifestyle changes, is a promising therapy in adolescents with obesity.

Read the full article at Kelly et al. 2020 New England Journal of Medicine doi: 10.1056/NEJMo1916038

Intestinal gluconeogenesis prevents non-alcoholic fatty liver disease

Hepatic steatosis is associated with obesity and can cause serious health problems, including inflammation, fibrosis and compromised liver function – collectively termed non-alcoholic fatty liver disease (NAFLD). Intestinal gluconeogenesis (IGN) was recently identified as counteracting hepatic lipid accumulation and the development of NAFLD. IGN occurs in response to protein- or fibre-enriched diets, or after gastric bypass surgery for obesity.

Vily-Petit et al. used mice with intestinal overexpression of glucose-6-phosphatase, the rate-limiting enzyme of gluconeogenesis, to examine the effects of IGN independently of nutritional or surgical intervention. These mice showed a decreased body weight gain, preserved glucose homeostasis, reduced hepatic lipid accumulation and attenuation of hepatic inflammation compared with wild type mice with or without a nutritional challenge. The underlying mechanism was found to be increased local sympathetic innervation, leading to decreased hepatic lipogenesis and lipid uptake.

The authors suggest that this gut-brain-liver neural circuit could be a target for potential NAFLD therapies.

Read the full article at Vily-Petit et al. 2020 Gut doi: 10.1136/gutjnl-2019-319745

Accelerated biological ageing in young adults with Prader–Willi syndrome

Adults with Prader–Willi syndrome (PWS) are at increased risk of developing age-associated diseases early in life, including diabetes mellitus, cardiovascular disease and cognitive decline, with increased mortality. Telomere shortening is considered to be involved in the progressive time-dependent functional decline of tissues.

Donze et al. investigated leucocyte telomere length (LTL), a marker of biological age, in 47 young adults with PWS compared with healthy young adults of similar age and also with growth hormone (GH)-treated young adults born small for gestational age (as the young adults with PWS all received GH) in a cross-sectional study. The median LTL was significantly shorter in PWS compared with both the other groups. In PWS, a lower LTL tended to be associated with a lower IQ. There was no association between LTL and duration of GH treatment, cumulative GH dose, or several risk factors for type 2 diabetes mellitus or cardiovascular disease.

The shorter telomeres may play a role in the accelerated biological ageing in PWS, independent of GH treatment.

Read the full article at Donze et al. 2020 Journal of Clinical Endocrinology & Metabolism doi: 10.1210/clinem/dgzt180
Addressing iodine deficiency

Michael Zimmermann considers the assessment, impact and best methods for eliminating preventable disease caused by iodine deficiency.

Iodine deficiency has multiple adverse effects on growth and development, due to what are termed the iodine deficiency disorders.\(^1\) Iodine deficiency remains one of the most common causes of preventable mental impairment worldwide.\(^2\)

Assessment

Four methods are generally recommended for the assessment of iodine nutrition: goitre, urinary iodine concentration, and blood concentrations of thyroid-stimulating hormone (TSH) and thyroglobulin.\(^1,2\)

Two methods are available for measuring goitre: neck inspection and palpation, and thyroid ultrasonography. Palpation of goitre has poor sensitivity and specificity, and measurement of thyroid volume by ultrasonography is preferable. Age- and gender-specific references are available for 6- to 12-year-old children.\(^2\)

Because over 90% of ingested iodine is excreted in the urine, the urinary iodine concentration is an excellent indicator of recent iodine intake. However, individual iodine intakes and urinary iodine concentrations are highly variable from day to day. Urinary iodine concentration is therefore not a good individual biomarker, but is recommended for populations.\(^2\) Dried blood spot and/or serum thyroglobulin has been shown to be a sensitive measure of iodine status, and an international reference range and a reference standard for children are available.\(^2\)

Effects of deficiency

The most serious adverse effect of iodine deficiency is damage to the fetus.\(^3\) Maternal thyroxine crosses the placenta before onset of fetal thyroid function at 10–12 weeks and represents up to 20–40% of thyroxine measured in cord blood at birth. Normal levels of thyroid hormones are required for neuronal migration and myelination of the developing brain, and lack of iodine irreversibly impairs brain development. Severe iodine deficiency in utero causes a condition characterised by gross mental retardation, along with varying degrees of short stature, deaf mutism and spasticity that is termed cretinism.\(^1\)

The potential adverse effects of milder iodine deficiency during pregnancy are unclear. Some observational studies have found that mild iodine deficiency in pregnancy predicts impaired cognitive development in the offspring,\(^4\) while others have not. In Europe, several randomised controlled trials of iodine supplementation in mild-to-moderately iodine-deficient pregnant women have been conducted.\(^4\) Iodine reduced maternal and newborn thyroid size, and, in some, decreased maternal TSH. However, none of the trials showed benefits for maternal and newborn total or free thyroid hormone concentrations.\(^4\) A recent randomised multicentre intervention trial that provided mildly iodine-deficient pregnant women with iodine supplements or placebo did not find benefits for offspring development at age 5–6 years.\(^5\)

Even mild iodine deficiency during childhood has detrimental effects on cognition. Moderately iodine-deficient 10- to 12-year-old European children (n=310) were randomised to receive either iodine supplements or placebo. Iodine treatment for 24 weeks significantly improved performance in tests of information processing, fine motor skills and visual problem solving.\(^6\) In mildly iodine-deficient New Zealand children (n=184), randomly assigned to receive iodine supplements or placebo for 28 weeks, the overall cognitive score of the iodine-supplemented group was significantly higher than that of the placebo group.\(^7\) Thus, in children born and raised in areas of iodine deficiency, cognitive impairment is at least partially reversible by iodine repletion.

Iodine status is also a key determinant of thyroid disorders in adults. Increased iodine intake in iodine-deficient adults is associated with a decrease in toxic nodular goitre, but a small increase in the prevalence of subclinical hypothyroidism and thyroid autoimmunity.\(^8\)

Treatment

The International Child Development Steering Group identified iodine deficiency as one of four key global risk factors for impaired child development, where the need for intervention is urgent.\(^9\) In nearly all countries, the best strategy to control iodine deficiency is salt iodisation: one of the most cost-effective ways to contribute to economic and social development. When salt iodisation is not possible, iodine supplements can be targeted to vulnerable groups, such as women of reproductive age and children.\(^10\)

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References
Central hypothyroidism: clinical management

This rare disease presents particular challenges in diagnosis and treatment, as Paolo Beck-Peccoz explains.

Central hypothyroidism (CeH) is a rare disease. Its global prevalence ranges from 1 in 20 000 to 1 in 80 000 individuals. Among all cases of hypothyroidism, CeH accounts for only 1 in 1000 hypothyroid patients. The term CeH encompasses several hypothalamic and/or pituitary disorders that may alter the normal thyroid-stimulating hormone (TSH) control of thyroid function. The insufficient stimulation of an otherwise normal thyroid gland results in a variable clinical and biochemical picture, spanning mild to severe hypothyroid conditions. Indeed, the precise pathological mechanisms leading to CeH are still undetermined, though three general mechanisms can be hypothesised:
- reduced pituitary reserve of TSH
- impaired thyrotroph stimulation, and
- reduced biological activity of secreted TSH molecules.

Aetiology

CeH can be acquired, as in the case of lesions at the pituitary and/or hypothalamic level due to diseases which are invasive (macroadenomas, craniopharyngiomas, gliomas, germinomas, etc.), immunologic (lymphocytic hypophysitis, IgG4-related hypophysitis, treatment with anti-CTLA4 antibodies, etc.), infiltrative (sarcoïdosis, histiocytosis X, haemochromatosis) or infectious (tuberculosis, mycoses, syphilis), as well as head trauma, pituitary apoplexy, Sheehan syndrome and iatrogenic causes (cranial surgery, treatment with bexarotene, mitotane, etc.).

Moreover, CeH may be congenital, mainly due to a genetic defect in hypothalamic or pituitary cells. Indeed, mutations in more than 19 genes have so far been reported to cause CeH.

Lastly, CeH can be isolated but, in the majority of patients, it is associated with combined pituitary hormone deficiency whenever the defect involves other pituitary cell lineages.

Diagnosis

The diagnosis of CeH may be difficult, as the hypothyroidism is less severe than expected and its manifestations are often masked by concomitant pituitary defects. Therefore, only the identification of low circulating levels of free thyroxine (FT4) together with low/normal serum TSH concentrations are indicative of the presence of CeH.

Nonetheless, attention must be paid to factors that could lead to the misdiagnosis of CeH patients:
- Methodological interference in FT4 measurement, leading to erroneously high serum FT4 values, may be seen if anti-T4 autoantibodies or abnormal T4 transport protein is present. In this situation, the interference masks the presence of CeH. It has been suggested that ‘two-step’ assays or equilibrium dialysis is the most reliable method for FT4 measurement.
- Similarly, methodological interference by circulating heterophilic antibodies may affect TSH measurement performed by an immunometric ‘sandwich’ assay, thus leading to falsely increased serum TSH levels. In this situation, a diagnosis of primary hypothyroidism could be made, thus masking the presence of CeH.

Furthermore, neonatal screening for congenital hypothyroidism made only on the basis of TSH measurement, without concomitant analysis of serum T4, fails to detect congenital CeH. Along the same lines, the routine use of the TSH reflex method, as a first-line test for screening thyroid function, renders it impossible to identify patients with CeH. Lastly, low serum FT4 levels and normal TSH concentrations may be present in patients with systemic non-thyroidal illness, thus mimicking a non-existent state of CeH.

Treatment

The treatment of CeH is based on levothyroxine (LT4) substitutive therapy and should be started only after exclusion of an associated hypocortisolism or under accurate steroid replacement. The aim of treatment is to restore normal levels of circulating thyroid hormones. The suggested doses of LT4 are 1.2–1.6 µg/kg body weight per day in CeH adults, while much higher doses, not different from those used in congenital primary hypothyroidism, should be administered in children with CeH. LT4 therapy should be started at a dose of 25µg and then gradually increased.

The measurement of serum FT4 levels is the best approach to evaluate the adequacy of LT4 treatment, if blood samples are drawn before the ingestion of LT4 tablets. Indeed, serum TSH concentrations cannot be used in monitoring LT4 adequacy, as they are suppressed even during low dose LT4 treatment. The measurement of serum TSH and free tri-iodothyronine is recommended when insufficient or excessive LT4 replacement is suspected.

Values of FT4 levels in the upper limit of the normal range is the target of LT4 treatment in CeH patients. Since growth hormone (GH) deficiency can mask subclinical forms of CeH, more frequent control of serum FT4 levels should be performed in patients treated with recombinant human GH. Interestingly, this effect on the hypothalamic-pituitary-thyroid axis is present only in CeH patients with combined pituitary hormone deficiencies and partial impairment of thyrotroph function, and is not present in patients with idiopathic isolated GH deficits.

Paolo Beck-Peccoz
Emeritus Professor, University of Milan, Italy

References
Hypothyroidism and resistance to levothyroxine

José Moreno provides an update on the most recent understanding of exogenous thyroid hormone resistance in hypothyroidism.

Levothyroxine (LT4) is currently the most extensively used formulation for the treatment of hypothyroidism worldwide. It is a safe and efficient drug to restore the euthyroid state in the majority of hypothyroid patients, including children with congenital hypothyroidism.\(^1\)

However, evidence has accumulated from adult endocrinology that a form of ‘resistance’ to exogenous thyroid hormone (RETH) is present in 5–10% of the hypothyroid population, particularly in patients who have undergone thyroidectomy.\(^2,3\) Despite correct compliance with LT4, the affected patients complain persistently of symptoms like lethargy, concentration deficits, anxiety and nervousness, comprising a state of poor well-being.

The European and American Thyroid Associations recognised this phenomenon, and independently published guidelines on how to deal with the problem, including recommendations to modify the substitution strategy from T4 to combined T4+tri-iodothyronine (T3), under given clinical circumstances.\(^2,3\) These guidelines are important, since serum thyrotrophin and free T4 (the most common parameters used to monitor hypothyroidism) may appear normal, making resistance to LT4 at risk of being overlooked in clinical practice.

The situation in paediatrics

One can reasonably wonder how this phenomenon applies to paediatric endocrinology care. Can RETH occur exclusively in hypothyroid adults and not in children using the same medication? To what extent can we assume that hypothyroid children and adolescents who have undergone thyroidectomy (for goitre, Graves’ disease or thyroid cancer) are ‘protected’ from experiencing RETH? And, as a particular paediatric case, how may RETH affect children with congenital agenesis of the thyroid gland?

In the absence of an international consensus on how to best detect RETH, it is conceivable that paediatricians face the additional challenge of suspecting RETH in hypothyroid children under LT4 who cannot properly communicate their state of well-being.

Insights into pathophysiology

A comprehensive pathophysiology of RETH is not fully established. But the fact that hypothyroid-like symptoms are concomitant with ‘euthyroidism in serum’\(^4\) led to the hypothesis that RETH generates a type of hypothyroidism that only exists in the tissues. Activation and inactivation of thyroid hormone is performed in local tissues by three different selenoenzymes: the iodothyronine deiodinases D1, D2 and D3. While D1 and D2 convert T4 into T3 (the active form of thyroid hormone), D3 converts T4 and T3 into reverse-T3 and T2 (3,5-di-iodothyronine), inactive metabolites for target gene transcription (Figure).

Interestingly, Dio2 knockout mice present pituitary resistance to the effects of exogenous T4,\(^6\) supporting the idea that RETH and deiodinase defects could also be causally linked in humans. However, no defects have yet been found in Dio1, Dio2 or Dio3 genes encoding the human deiodinases.

Recently, two major breakthrough findings shed light on the cause and mechanisms of the resistance to LT4 in humans and mice. Castagna et al.\(^4\) showed that a common human polymorphism in Dio2 (Ala92Thr D2) reduces the activity of the enzyme in vitro, and generates less T3 than the wild type enzyme under proper stimuli.\(^5\) In parallel, they showed for the first time that thyroidectomised adult patients on LT4 who harbour Ala92Thr D2 had significantly lower T3 in serum, compared with their pre-surgery levels.\(^5\) The findings unequivocally show that functional Dio2 polymorphisms can impact the metabolism of thyroid hormone, and are reflected in serum parameters of large clinical series.

The question remains of whether such polymorphisms can actually hamper the euthyroid state of tissues, especially the brain, in hypothyroid patients on LT4. Addressing this question, a seminal paper from Jo et al.\(^7\) showed that mice with brain-specific expression of the Ala92-variant of the D2 enzyme do present brain hypothyroidism.\(^7\) They further showed that the D2-variant protein is abnormally retained in the endoplasmic reticulum (ER), causing ER stress, which triggers excess degradation of the mutant deiodinase. Of high relevance,
Thyroid nodules and differentiated thyroid cancer

Andrew Bauer brings us up to date with the latest approaches in diagnosis and management of paediatric thyroid cancer.

An increasing number of paediatric patients are referred for evaluation and management of thyroid nodules and differentiated thyroid cancer (DTC). With an excellent prognosis for the majority of those who have DTC, therapy aims to optimise outcomes while reducing complications.

Over the last decade, we have gained more data on somatic, oncogenic driver mutations. This knowledge provides opportunities to improve the accuracy of diagnosis, to potentially stratify surgery, and to treat selected patients with morbidly invasive disease at presentation or who develop refractory disease after traditional therapy.1,2 While there may be differences in management based on resources, as well as differing opinions in the approach to care, treatment complications can be reduced by referral to regional, high-volume, paediatric thyroid centres.3

Diagnostic evaluation
Thyroid ultrasound is the preferred and most informative method for evaluating thyroid nodules. Nodule characteristics associated with an increased risk of malignancy include solid composition, hypoechoigenicity (dark grey, similar to the cervical strap muscles), lobulated or irregular margins, presence of punctate echogenic foci, and evidence of extra-thyroidal extension (best discerned at the anterior edge of the thyroid).4 Characteristics associated with benign cytology include highly cystic content (>50%) and spongiform appearance.5

There are several systems that may be used to stratify the nodules that should undergo fine needle aspiration (FNA). These include the American College of Radiology Thyroid Imaging Reporting and Data System (TI-RADS), the European Thyroid Association (ETA) TI-RADS, and others.6 Preliminary data in paediatrics suggest that the systems are useful but not independently sufficient to identify thyroid malignancy. Across all age groups, the presence of cervical lymphadenopathy is important, and should overrule the likelihood of thyroid malignancy in nodules that would otherwise be considered benign based on ultrasound characteristics, or too small to pursue FNA.

Similar to ultrasound, there are several systems for predicting the risk of malignancy in thyroid FNA. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)7 and the ETA guidelines,8 amongst others, may be used in paediatrics with the same sensitivity, specificity and accuracy as in adults.9,10 However, while the results of the FNA are similarly used to stratify an appropriate management plan, there appears to be an increased risk of malignancy for paediatric patients across all cytopathologic classifications. In adults, benign cytology is associated with a 0–3% risk of malignancy, while in paediatrics the risk of malignancy may be as high as 10%.11 For nodules in TBSRTC category 3 (atypia or follicular lesion of undetermined significance), category 4 (follicular neoplasm), or category 5 (suspicious for malignancy), the risk of malignancy in paediatrics may be as high as 28%, 58% and 100%, compared with 18%, 40%, and 60% respectively in adults.11,12

References
1. Krause et al 2015 Best Practice & Research Clinical Endocrinology & Metabolism 29 399–413.
2. Warris et al 2012 European Thyroid Journal 1 55–71.

Supplemental oncogenic profile testing is the only form of molecular testing that has clinical utility to predict an increased risk for malignancy in patients under 19 years of age.

differentiated thyroid cancer

they used rodent behavioural tests to show that the T3-dependent brain hypothyroidism caused a phenotype of poor memory, anxiety and fear, which very much brings to mind the psychological complaints in RETH patients.

Clinical application
From the translational perspective, the most promising news is that the ‘hypothyroid-brain phenotype’ of Ala92-D2 mice could be reversed by the administration of T4+T3 (or an ER chaperone) but not by T4, which could not resolve symptoms alone.

These elegant pieces of work represent food-for-thought to endocrinologists, but especially to paediatric endocrinologists, responsible for the care of hypothyroid children who cannot comprehensively communicate the typical symptoms of RETH.

Firm answers can only come from paediatric-specific clinical research, including the identification of hormone biomarkers allowing safe diagnosis of RETH and the investigation of genetic and molecular drivers underlying the resistance to exogenous thyroid hormone in at least a proportion of hypothyroid children.

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References
1. Krause et al 2015 Best Practice & Research Clinical Endocrinology & Metabolism 29 399–413.
2. Warris et al 2012 European Thyroid Journal 1 55–71.
Supplemental oncogenic profile testing is the only form of molecular testing that has clinical utility to predict an increased risk for malignancy in patients under 19 years of age. In children, the presence of a thyroid oncogene mutation (BRAFV600E) or fusion (RET/PTC, NTRK-fusion and others) in an indeterminate FNA specimen is associated with a near 100% likelihood of papillary thyroid cancer (PTC). The presence of other mutations, including those in RAS, DICER1 and PTEN, may be associated with both benign and malignant disease. For these mutations, until additional molecular markers are available, diagnostic lobectomy for unilateral nodules with ‘indeterminate oncogenes’ should be pursued to determine the histologic diagnosis.

Surgical and medical management
In an effort to minimise the risk of complications, and to ensure the surgeon understands the disease within the age-specific population, thyroid surgery should be performed by a high volume thyroid surgeon, defined within the age group of the patient undergoing surgery.

Most children with PTC should undergo near-total thyroidectomy. Prophylactic central neck lymph node dissection can be performed in an effort to define the invasive behaviour of the disease and stratify radioactive iodine treatment. With extremely low disease-specific mortality, including encapsulated follicular variant PTC and minimally invasive follicular thyroid cancer, lobectomy may suffice to achieve surgical remission.

RAI is a highly effective, targeted medical therapy to treat persistent post-surgical disease. Ablative RAI therapy is effective in destroying the thyroid remnant as well as potential micrometastases to central neck lymph nodes, an approach that may benefit patients with PTC who do not undergo prophylactic central neck lymph node dissection. With extremely low disease-specific mortality for paediatric patients with PTC, benefit should be defined by decreased persistent or recurrent disease. For patients with pulmonary metastasis, RAI may result in remission from disease in less than 50–75% of patients, with the majority of patients requiring multiple doses of RAI.

For patients with minimal, persistent, cervical lymph node disease, ultrasound-guided, percutaneous ethanol or radiofrequency ablation may be considered.

Future directions
Knowledge of the somatic oncogenic driver mutation is becoming increasingly important for the diagnosis of thyroid nodules with indeterminate cytology, as well as for the prediction of clinical behaviour and response to therapy, and for the selection of systemic therapy.

For patients who present with evidence of recurrent laryngeal nerve paralysis, encasement of great vessels, evidence of aggressive/locoregional tract invasion or with pulmonary metastasis associated with hypoxia, neoadjuvant systemic therapy should be considered, in an effort to reduce surgical morbidity. For patients who develop progressive DTC that is refractory to RAI and not amenable to surgery, adjuvant systemic therapy should be considered, based on anatomic progression.

Given the potential for significant side effects, and limited experience in using these agents in children and adolescents, multi-centre, collaborative studies are needed to better define the timing for initiation, selection of drug, monitoring and adjustment of therapy, so that we optimise outcomes while minimising the risk of side-effects and adverse events.

In conclusion
In the 20th century, the evaluation of thyroid nodules and treatment of thyroid cancer relied on cytologic, histologic and biochemical data. In 2014, The Cancer Genome Atlas (TCGA) proposed that incorporation of molecular subtype, classified by oncogenic driver groups, may improve our ability, over pathologic classification, to predict tumour behaviour.

Preliminary data in paediatrics suggest that we should pursue a similar approach, that early identification of the oncogenic driver mutation may provide improved accuracy of diagnosis, as well as an opportunity to stratify surgery and optimise medical care. We are extremely fortunate that the majority of paediatric patients with DTC experience low disease-specific mortality. However, we are obliged to continue to find better opportunities to improve care, to reduce complications while maintaining a low risk of persistent and recurrent disease.

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17. Francis et al. 2015 Thyroid 25 716–759.
Future meetings
See [www.eurospe.org/meetings](http://www.eurospe.org/meetings) for details of all future meetings

**MAY 2021**
- **59th Annual ESPE Meeting**
  7–9 May 2021
  Liverpool, UK
- **11th International Meeting of Pediatric Endocrinology**
  25–28 September 2021
  Buenos Aires, Argentina
- **60th Annual ESPE Meeting**
  September 2022
  Rome, Italy
- **61st Annual ESPE Meeting**
  September 2023
  The Hague, The Netherlands

**OCTOBER 2021**
- **ESPE Science Symposium**
  29–30 October 2021
  Nijmegen, The Netherlands

**POSTPONED TO 2021**
- **ESPE Winter School**
- **ESPE Caucasus & Central Asia School**
- **ESPE Maghreb School**
- **ASPED-ESPE Endocrine Academy**
- **Joint EASD/ISPAD/ESPE Postgraduate Education Course**

**DEADLINES**

**JUNE**
- Andrea Prader Committee vacancy applications – 1 June 2020
- Clinical Practice Committee vacancy applications – 1 June 2020
- Communications Committee vacancy applications – 1 June 2020
- Diabetes, Obesity & Metabolism School applications – 3 June 2020

**JULY**
- Early Career Scientific Development Grant applications – 31 July 2020

**SEPTEMBER**
- Clinical Fellowship applications – 30 September 2020

**OTHER EVENTS**