Thyroid

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In the last 12 months significant advances were achieved in important areas of thyroid research. Clinical outcome studies increased our knowledge on long-term effects of congenital hypothyroidism on fertility, maternal thyroid disorders during pregnancy on infant's cognitive development and anti-thyroid medication in children with autoimmune hyperthyroidism. Developmental research convincingly established the role of micro-RNAs for normal thyroid development and function, and elucidated new molecular mechanisms of thyroid hormone receptor-dependent pulmonary development. This year's highlight in thyroid genetics was the description of a new form of thyroid hormone resistance due to mutations in the thyroid hormone receptor- α subunit. This chapter aims at giving a representative overview of the key publications in thyroidology.

Clinical trials

Antenatal thyroid screening and childhood cognitive function

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Background: Thyroid hormone levels during pregnancy have been reported to be crucial for the cognitive function of the offspring.

Methods: The authors conducted a randomized trial in pregnant women at a gestation of 15 weeks 6 days, or less. The women provided blood samples for measurement of thyrotropin (TSH) and free thyroxine (free T₄) and were assigned either to a screening group (in which measurements were obtained immediately) or a control group (in which serum was stored and measurements were obtained shortly after delivery). Women with positive findings in the screening group (TSH levels above the 97.5th percentile, free T₄ levels below the 2.5th percentile, or both) were assigned to 150 µg levothyroxine per day. The primary outcome was IQ at 3 years of age in children of women with positive results, as measured in a blinded fashion by psychologists.

Results: The study was able to obtain a large group of 21,846 women with blood samples at a median gestational age of 12 weeks 3 days: 390 women in the screening group and 404 in the control group tested positive. The median gestational age at the start of levothyroxine treatment was 13 weeks 3 days. Children of women with positive results had mean IQ scores of 99.2 and 100.0 in the screening and control groups, respectively (difference 0.8; 95% confidence interval –1.1 to 2.6; $p = 0.40$). The proportions of children with an IQ <85 were 12.1% in the screening group and 14.1% in the control group (difference 2.1 percentage points; 95% CI –2.6 to 6.7; $p = 0.39$).

Conclusions: The authors concluded that antenatal screening (at a median gestational age of 12 weeks 3 days) and maternal treatment for hypothyroidism did not result in improved cognitive function in children at 3 years of age.

Mild maternal thyroid dysfunction at delivery of infants born ≤ 34 weeks and neurodevelopmental outcome at 5.5 years

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Background: Many publications have demonstrated that mild maternal thyroid dysfunction during early pregnancy is associated with poor neurodevelopment in affected offspring. The authors did not find studies that focused on preterm infants. They wished to describe the relationship between mild maternal thyroid dysfunction at delivery of infants born ≤ 34 weeks of gestation and their neurodevelopment at 5.5 years of age.

Methods: The authors performed a follow-up study evaluating the association of delivery levels of maternal TSH, and free T_4 (FT_4) in 143 women with McCarthy Scale scores adjusted for 26 confounders of neurodevelopment in their 166 children.

Results: The authors observed after adjustment for confounders significant 3.2-, 2.1-, and 1.8-point decrements, respectively, in general cognitive index, verbal subscale, and the perceptual performance subscale for each milliunit per liter increment in maternal TSH. After adjustment, significant associations were found with maternal FT_4 for the general cognitive index, motor scale, and quantitative subscale; each picomole per liter decrease in FT_4 was associated with a significant increase of general cognitive index (+1.5 points), motor scale (+1.7 points), and quantitative subscale (+0.9 points), respectively.

Conclusions: The authors concluded that higher maternal levels of TSH at delivery of infants born preterm were associated with lower scores on the general cognitive index at 5.5 years of age.

Previous studies have suggested that maternal hypothyroxinemia during pregnancy can negatively affect cognitive function of the children. Two years ago a large-scale study demonstrated the consequences of low maternal T_4 on the offspring cognition and correlated the whole range of FT_4 during early pregnancy with cognition in early childhood [1].

Up to now there was a paucity of data providing evidence for beneficial outcome of infants of hypothyroxinemic mothers after iodine or T_4 supplementation in early gestation. Therefore, intervention studies with iodine or thyroxine supplementation were needed. Lazarus et al. realized a large-scale prospective controlled randomized study in comparing treatment versus observation in early gestation with puzzling results. The study did neither find a significant difference in child IQ at the age of 3 years when starting treatment at 13 weeks of gestation nor was the proportion of children with IQ < 85 different in the screening group versus the control group. Was the time point of screening and treatment too late? Calvo et al. found that in early (5–12 GW) embryonic fluids FT_4 concentrations were at least one third of those in their euthyroid mothers. They concluded that the availability of FT_4 for embryonic and fetal tissues would decrease in hypothyroxinemic women and may result in adverse effects on the timely sequence of developmental events in the human fetus as early as the first trimester [2]. Could postnatal iodine deficiency be a confounding factor that may affect the results? (See Vanderpump et al. on iodine status of UK schoolgirls, below in this chapter.) Indeed, studies demonstrated that the IQ of schoolchildren in a developed country can be influenced by iodine intake [3]. For the moment, the Lazarus study does not provide new arguments for universal screening of maternal hypothyroidism, but further trials are ongoing (<http://www.clinicaltrials.gov/ct/show/NCT00388297>).

Differences between the published studies on neurodevelopment may be due to several factors: (1) definition of maternal hypothyroidism (elevated TSH, hypothyroxinemia or both?), (2) time point of thyroid status assessment during pregnancy, (3) age and tools of neurodevelopmental assessment of the child, (4) term versus preterm infants. In this context, Williams et al. confirmed the association between maternal TSH levels, as was shown earlier in term neonates [4], but also FT_4/T_4 and neurodevelopmental outcome in preterm infants.

Positive impact of long-term antithyroid drug treatment on the outcome of children with Graves' disease: national long-term cohort study

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Background: Drug-based therapy is usually the initial treatment for Graves' disease (GD) hyperthyroidism in children. The objective of the authors was to assess the effect of long-term carbimazole therapy on GD remission in children and its determinants.

Methods: The authors included 154 children newly diagnosed with GD between 1997 and 2002 in an observational prospective multicenter follow-up cohort study. The intention was to treat patients with three consecutive courses of carbimazole, each lasting 2 years. Definitive treatment was performed in cases of poor compliance with antithyroid drug (ATD) treatment, thyrotoxicosis relapse, or major adverse effects of ATD treatment. The authors used remission for at least 18 months after the completion of each course of ATD treatment as major outcome measure.

Results: The median duration of follow-up was 10.4 (9.0–12.1) years. Overall estimated remission rates (95% confidence interval) 18 months after the withdrawal of ATD treatment increased with time and were 20 (13–26), 37 (29–45), 45 (35–54), and 49 (40–57)% after 4, 6, 8, and 10 years of follow-up, respectively. An independent positive effect of less severe forms of hyperthyroidism at diagnosis (sub-hazard ratio of 1 for patients with $FT_4 < 35$ pmol/l vs. 0.4 (0.20–0.80) for $FT_4 \geq 35$ pmol/l; $p = 0.01$) and of the presence of other autoimmune conditions (subhazard ratio of 2.23 (1.19–4.18); $p = 0.01$) was documented on remission rate after medical treatment.

Conclusion: About half the patients achieved remission after carbimazole discontinuation, and there seems to be a plateau in the incidence of remission achieved after 8–10 years of ATD therapy.

This is a unique long-term follow-up study of a cohort of children affected by autoimmune hyperthyroidism. The first study on this cohort published in 2008 showed the following results which are worth mentioning [5]. The overall estimated relapse rate for hyperthyroidism was 59% (95% confidence interval 52–67%) at 1 year and 68% (95% confidence interval 60–76%) at 2 years after the end of treatment. Multivariate analysis showed that the risk of relapse was higher for patients of non-Caucasian origin (hazard ratio (HR) = 2.54, $p < 0.001$), with high serum thyroid-stimulating hormone receptor antibodies (TRAb) (HR = 1.21 by 10 U, $p = 0.03$) and FT_4 (HR = 1.18 by 10 pmol/l, $p = 0.001$) levels at diagnosis. Conversely, relapse risk decreased with increasing age at onset (HR = 0.74 per 5 years, $p = 0.03$) and duration of first course of ATD (HR = 0.57 per 12 months, $p = 0.005$). A prognostic score was constructed, allowing the identification of three different risk groups, with 2-year relapse rates of 46, 77, and 98%.

Interestingly, the presented study highlights the positive impact of lower initial severity of hyperthyroidism on remission in the long-term follow-up as observed in the short term. However, for unclear reasons, the multivariate analysis did not identify age at presentation, ethnicity and initial TRAb levels as related to remission rate in the long-term follow-up study.

The authors further suggest that children with autoimmune hyperthyroidism displaying good compliance without major adverse effects of antithyroid drugs may be offered continuous medical treatment up to 8–10 years before planning definitive treatment. Certainly this conclusion will be challenged by pediatric endocrinologists offering much earlier an ablative therapy for children with Graves' disease.

Is the incidence of congenital hypothyroidism really increasing? A 20-year retrospective population-based study in Quebec

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Background: Changes in screening methods for congenital hypothyroidism (CH) may explain the reportedly increasing frequency of CH in the United States. In Quebec, the same initial TSH cutoff (15 mU/l) has been used for the last 20 years, but in 2001, the cutoff was decreased from 15 to 5 mU/l for the second test, which is requested when TSH is intermediate (15–30 mU/l) on the first.

Methods: The authors aimed (1) to assess the incidence of CH over the last 20 years in Quebec using a population-based retrospective study and (2) to compare the incidences of CH by etiology based on thyroid scintigraphy between 1990–2000 and 2001–2009.

Results: Of 1,660,857 screened newborns over 20 years, 620 had CH (incidence 1:2,679). Scintigraphy revealed dysgenesis ($n = 389$, 1:4,270), either due to ectopy ($n = 290$) or athyreosis ($n = 99$), goiter ($n = 52$, 1:31,940), normal-size gland in situ ($n = 115$, 1:14,442), and unknown morphology ($n = 64$, 1:25,950). 49 additional cases were identified with the new screening algorithm (i.e. 25 normal-size gland in situ, 12 unknown etiology, 10 ectopies, and 2 goiters). Consequently, the incidence of normal-size gland in situ or of unknown etiology more than doubled (1:22,222 to 1:9,836, $p = 0.0015$, and 1:43,824 to 1:17,143, $p = 0.0018$, respectively) but that of dysgenesis and goiter remained stable.

Conclusion: The authors demonstrated that the incidence of CH is influenced by minimal changes in TSH screening cutoffs. Decreasing the cutoffs resulted in identification of additional cases that have predominantly functional disorders (thyroid in situ).

The newborn screening program in Quebec requests a second specimen in babies who have borderline TSH elevation between 15 and 30 mU/l (whole blood) on the first test. Between 1990 and 2000, when the TSH cutoff on the second test was >15 mU/l, the overall incidence of CH was 1:2,898. Between 2001 and 2009, when the TSH cutoff on the second test was lowered to >5 mU/l, the incidence rose to 1:2,450. Lowering the cutoff from 15 to 5 mU/l led to the detection of 49 additional cases of congenital hypothyroidism. The investigators clearly established that the apparent increased incidence was in fact solely the result of the lowered TSH cutoff on the second test. Although the Quebec authors do not comment, one presumes that there were no significant changes in population demographics, as noted in the United States. The conclusion for the increased incidence in Quebec is in accordance with earlier reports [6, 7]. In addition, the majority of the additional cases detected with a lower TSH cutoff by these programs had a thyroid gland in situ. In their analysis of laboratory practices in US newborn screening programs, the authors concluded that ‘while different laboratory methods and screening practices affected the incidence rates, additional, unknown factors contributed to the reported increased rate’ [8]. The following questions are raised: What could be the exact cause of congenital hypothyroidism with thyroid in situ? Do mild cases of congenital hypothyroidism benefit from detection by newborn screening and early thyroid hormone treatment?

Hippocampal size and memory functioning in children and adolescents with congenital hypothyroidism

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Background: Selective and persistent neurocognitive weaknesses may be seen in children affected by congenital hypothyroidism (CH) despite early diagnosis and treatment after newborn screening. One area of particular weakness is memory, especially on tasks known to be mediated by the hippocampus. The

objective of the authors was to use magnetic resonance imaging to determine whether children and adolescents with CH have reduced hippocampal size and abnormal hippocampal growth patterns relative to peers and whether reduced hippocampal volumes in CH predict poor memory performance.

Methods: The authors included 35 CH patients and 44 controls aged 9–15 years in their study. All were assessed using standardized tests of intelligence and verbal and visual memory and received a magnetic resonance imaging scan. Parents completed a questionnaire of their everyday memory functioning (EMF). Right and left hippocampal volumes were measured by manual tracing.

Results: CH subjects scored significantly below controls on indices of verbal but not visual memory. EMF was also affected for some aspects more than for controls. CH subjects also had smaller hippocampal volumes, particularly on the left side. Unlike controls, who showed a positive relationship between age and hippocampal volumes, age was unrelated to hippocampal size in CH. Structure-function correlations revealed significant relationships between hippocampal volumes and EMF in controls and modest correlations between hippocampal volumes and memory test scores but not EMF in CH.

Conclusions: The authors concluded that compromised hippocampal development in CH may contribute to some of the memory weaknesses of the patients affected by CH.

The authors have a long-standing interest in neurocognitive function in patients with congenital hypothyroidism. With specific testing, subtle neuropsychological anomalies can be demonstrated in affected children who will appear as normal for the pediatrician. For those 'apparently normal' patients, the consequences for their daily life may be minor. However, the hippocampus is very much related to ageing and diseases of ageing such as neurodegenerative disorders [9]. Will patients with congenital hypothyroidism show a different ageing process than controls? One wonders whether we have really closed the 'developmental gap with early high dose levothyroxine treatment' as stated 16 years ago [10]. Is there still room for improvement, especially by trying to minimize the impact of the lack of thyroid hormone in utero?

Fecundity in young adults treated early for congenital hypothyroidism is related to the initial severity of the disease: a longitudinal population-based cohort study

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Background: Hypothyroidism, if untreated, is a source of impaired fecundity. Screening programs for CH have been running for only the last 30 years in most industrialized countries. Therefore, patients treated early for CH have yet to be evaluated in adulthood. The authors' objective was to assess the fecundity of young adults treated early for CH and its determinants.

Methods: Of 1,748 subjects diagnosed with CH in the first 10 years after the introduction of neonatal screening in France, 1,158 completed a questionnaire on fecundity at a mean age of 25.3 years. This self-administered questionnaire focused on first attempts to have a child and time to pregnancy. The control group was that used in an analogous study on subjects born between 1971 and 1985. Fecundability hazard ratios (HR) were adjusted for known fecundity confounders (age, smoking, and reproductive history).

Results: Globally, fecundability was similar for the CH and control group. However, women with athyrosis, with absence of bone maturation at the knee epiphyseal ossification centers, and a low serum-free T₄ concentration at diagnosis (<5 pmol/l), representing the most severe forms of CH, were associated with lower fecundity: HR = 0.68 (0.50–0.98) (p = 0.02), HR = 0.65 (0.45–0.94) (p = 0.02), and HR =

0.70 (0.50–0.97) ($p = 0.03$), respectively. However, fecundability was not associated with age at the start of treatment, initial levothyroxine dose, or the adequacy of hypothyroidism control.

Conclusion: Fecundity was lower in women suffering from the most severe form of the disease.

These data originate from a unique population-based, large-scale study of young adults affected by congenital hypothyroidism. The systematic study of this cohort in comparison with an appropriate control group provides important information on long-term health and socioeconomic status of adults with CH [11]. One could have postulated that patients with CH might have a lower fecundity than the control population. Counter-intuitively, the overall fecundity was comparable in CH patients with that in controls. Only the subgroup of the most affected women, suffering from athyreosis, had a lower fecundity, although fecundity was not associated with age at start of treatment, initial LT_4 dose, or control of hypothyroidism after 15 days of treatment. Given the observational nature of the study, the impact of in utero hypothyroidism on the hypothalamus-pituitary-ovary axis remains unclear.

Genetics: new findings in 'old' genes

Frequent TSH receptor genetic alterations with variable signaling impairment in a large series of children with nonautoimmune isolated hyperthyrotropinemia

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Background: Partial TSH resistance, characterized by isolated nonautoimmune hyperthyrotropinemia (NAHT) has been associated with heterozygous mutations in the TSH receptor gene (TSHR). The authors aimed to investigate the prevalence and clinical impact of TSHR alterations in a large series of pediatric patients with NAHT.

Methods: The authors performed a prospective multicenter study which included 153 unrelated patients with NAHT aged <18 years. Patients with thyroid dysgenesis or major associated congenital defects were excluded from the study.

Results: The frequency of heterozygous nonpolymorphic TSHR variations was 11.8%. The authors identified seven previously undescribed variations: a frameshift (p.Q33PfsX46), one intronic (g.IVS4+2A→G), and five novel missense mutations (p.P162L, p.Y466C, p.I583T, p.I607T, and p.R609Q). The missense variations variably affected TSHR membrane expression and G(s) and/or G(q/11) signaling. Several variations cosegregated with NAHT in the affected families. Parameters of thyroid function were similar between affected and unaffected family members.

Conclusions: The authors concluded that nonpolymorphic alterations in the TSHR gene were commonly associated with isolated NAHT in young patients. This study confirmed that partial TSH resistance is the most frequent inheritable cause of isolated NAHT. The authors provided further evidence that besides the well-known defects in G(s) signaling, TSHR genetic alternations found in NAHT may frequently impair the G(q/11) pathway.

A mutation in the thyroid hormone receptor- α gene

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N Engl J Med 2012;366:243–249

Background: Thyroid hormones exert their effects through α (TR α 1) and β (TR β 1 and TR β 2) receptors.

Methods: The authors describe a child with classic features of hypothyroidism (growth retardation, developmental retardation, skeletal dysplasia, and severe constipation) but only borderline-abnormal thyroid hormone levels.

Results: Using whole-exome sequencing, they identified a de novo heterozygous nonsense mutation in a gene encoding thyroid hormone receptor- α (THRA) and generating a mutant protein that inhibits wild-type receptor action in a dominant negative manner.

Conclusions: Their observations are consistent with defective human TR α -mediated thyroid hormone resistance and substantiate the concept of hormone action through distinct receptor subtypes in different target tissues.

During the last 12 months, no new gene with relevant role in the hypothalamus-pituitary-thyroid axis has been identified. However, new insights on the genetic basis of resistance syndromes in the thyroid axis have been published. The first paper focused on TSH resistance. It provides data on prevalence of heterozygous nonpolymorphic TSHR gene variations in a large pediatric cohort of patients with nonautoimmune hyperthyrotropinemia detected either by neonatal screening or by repeatedly increased TSH values during childhood. The prevalence of TSH resistance due to heterozygous TSHR mutations was 12%, which is higher than in other recent studies with comparable inclusion criteria, suggesting that in some settings heterozygous TSHR mutations are up to now the most frequent genetic cause of nonautoimmune hyperthyrotropinemia [12]. Important for clinical practice, only one third of patients were detected by neonatal screening and about half had no affected family members.

The second paper describes the use of whole-exome sequencing to identify a new and very severe form of thyroid hormone resistance due to the first described mutation in the thyroid hormone receptor- α (THRA) gene. In direct contrast to the more typical patients with thyroid hormone resistance due to THRB mutations, the clinical phenotype in this case was characterized by marked clinical hypothyroidism in the context of slightly decreased thyroxine and increased T₃ levels. The lack of elevation in thyroxine levels appears to be attributable to the persistence of normal central THRB signaling. There was differential responsiveness of target tissues to thyroxine treatment. Especially, the tissues highly expressing THRA (bone, heart, intestine) showed thyroid hormone resistance with no improvement of growth, chronic constipation and heart rate despite thyroxine treatment, consistent with the genetic findings.

Thyroid and lung: mechanism of the year

Thyroid hormone receptor repression is linked to type I pneumocyte-associated respiratory distress syndrome

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Background: The lung epithelium mainly consists of type I pneumocytes, which mediate gas exchange, and type II pneumocytes, which produce surfactant proteins. Type II pneumocyte maturation is promoted

by glucocorticoids through the glucocorticoid receptor and its cognate ligand and this mechanism underlies the use of glucocorticoid administration to treat infant respiratory distress syndrome. In contrast, the pathway controlling the formation of type I pneumocytes is poorly understood. The study aimed to investigate the role of the co-repressor SMRT (silencing mediator of retinoid and thyroid hormone receptors) for type I pneumocyte differentiation.

Methods: The authors generated SMRT knock-in mice (SMRTmRID) that specifically disrupted the interaction between SMRT and nuclear receptors.

Results: SMRTmRID mice died shortly after birth from a previously unidentified acute respiratory distress syndrome resulting from an abnormal terminal differentiation of the type I pneumocyte, while showing normal type II pneumocyte function. While unresponsive to glucocorticoids, treatment with antithyroid hormone drugs (propylthiouracil or methimazole) completely rescued SMRT-induced respiratory distress syndrome, suggesting an unrecognized and essential role for the thyroid hormone receptor in lung development. The authors further showed that the thyroid hormone receptor and SMRT controlled type I pneumocyte differentiation through Klf2, which, in turn, seemed to directly activate the type I pneumocyte gene program.

Conclusions: The thyroid hormone receptor was identified as a second nuclear receptor involved in lung development, specifically involved in type I pneumocyte differentiation. The authors suggested a possible new type of therapeutic option in the treatment of respiratory distress syndrome that is unresponsive to glucocorticoids.

The role of thyroid hormone receptors in different tissues and organs has been thought to be well characterized. The presented study suggests a new role of the nuclear thyroid hormone receptor during a critical time window of embryonic lung development by rescuing disordered terminal differentiation of type I pneumocytes in SMRTmRID mice by maternal treatment with PTU and MMI. In summary, the authors showed that association of SMRT and the thyroid hormone receptor are crucial for the development of type I pneumocytes and that thyroid hormone signaling is mediated by Klf2 in the lung. Future studies focusing on lung development in thyroid hormone receptor-deficient mice will be of great importance to further support the thyroid hormone receptor-dependent mechanism of the presented results in SMRTmRID mice.

New concerns linked to iodine deficiency

Low iodine content in the diets of hospitalized preterm infants

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Background: Iodine is the limiting substrate for thyroid hormone synthesis. Hypothyroidism due to iodine deficiency is a frequent cause of mental retardation worldwide. Preterm infants have a lower iodine store than term infants, rendering preterm infants particularly vulnerable to the effects of iodine deficiency. Currently it is unknown whether the dietary iodine intake meets the requirement for hospitalized preterm infants. The authors aimed to measure the iodine content of enteral and parenteral nutrition products commonly used for hospitalized preterm infants and estimate the daily iodine intake for a hypothetical 1-kg infant.

Methods: Mass spectrometry was used to measure the iodine concentration of a representative selection of (1) preterm infant formulas, (2) samples of pooled donor human milk with or without human milk fortifiers, (3) enteral supplements, and (4) a parenteral amino acid solution and a soy-based lipid emulsion. The daily iodine intake provided by diets based on 150 ml/kg body weight/day of formula, donor human milk with or without human milk fortifies, and parenteral nutrition was calculated.

Results: Preterm formula provided 16.4–28.5 µg/day of iodine, whereas unfortified donor human milk provided only 5.0–17.6 µg/day. The other enteral supplements contained almost no iodine, nor did a parenteral nutrition-based diet.

Conclusions: Typical enteral diets for hospitalized preterm infants, particularly those based on donor human milk, provide less than the recommended 30 µg/day of iodine, and parenteral nutrition provides almost no iodine. Additional iodine fortification should be considered.

Iodine status of UK schoolgirls: a cross-sectional survey

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Lancet 2011;377:2007–2012

Background: Iodine deficiency is the most common cause of preventable mental impairment worldwide. It is defined by WHO as mild if the population median urinary iodine excretion is 50–99 µg/l, moderate if 20–49 µg/l, and severe if <20 µg/l. No contemporary data were available for the UK. The authors aimed to assess iodine status of the UK population.

Methods: In a cross-sectional survey, the iodine status of girls at 14–15 years of age was investigated in nine different regions. Urinary iodine concentrations and tap water iodine concentrations were measured in summer and winter 2009. Ethnic origin, postal code, and a validated diet questionnaire assessing sources of iodine were recorded.

Results: From 810 participants, 737 urine samples and 664 questionnaires of dietary habits were available. Median urinary iodine excretion was 80.1 µg/l (IQR 56.9–109.0). Based on urinary iodine excretion and according to WHO definitions, mild iodine deficiency was present in 51% (n = 379) of participants, moderate deficiency in 16% (n = 120), and severe deficiency in 1% (n = 8). Prevalence of iodine deficiency differed in the nine analyzed geographical regions. Tap water iodine concentrations were low or undetectable and were not positively associated with urinary iodine concentrations. Multivariable general linear model analysis confirmed independent associations between low urinary iodine excretion and sampling in summer (p < 0.0001), geographical region (p < 0.0001), and low intake of milk (p = 0.03).

Conclusions: The data of this cross-sectional study suggest that the UK is iodine-deficient. The presented results have drawn attention to an urgent need for a comprehensive investigation of UK iodine status and implementation of evidence-based recommendations for iodine supplementation.

Two papers raised concerns about unexpected risk of iodine deficiency in the pediatric age group in developed countries. The first paper focused on preterm infant diet, as only few data were available on iodine content in enteral and parenteral nutrition of preterm babies. Belfort et al. examined the iodine content of infant formulas, human milk donor samples with or without fortifier, and parenteral nutrients used for preterm infant nutrition. Neither formulas nor human milk at a calculated fluid intake of 150 ml/kg/day provided the recommended minimal dose of 30 µg/kg iodine per day. Particularly donor human milk and parenteral solutions were poor in iodine. These results raise the concern of inadequate iodine supply to preterm infants, especially when receiving donor human milk. However, the study did not assess iodine status in the preterm infant group. Besides additional iodine fortification, a pragmatic way of improving human donor milk iodine content would be to promote systematic intake of the daily recommended dose of 150 µg iodine in all lactating women, however even that target may be insufficient in some lactating women [13].

The second paper by Vanderpump presents data from a cross-sectional study of iodine status of adolescents from the UK. According to the authors, the UK was thought to be iodine-sufficient, although no iodine food or salt iodination program exists. The study was initiated as the authors observed insufficient use of iodized salt and increasing number of pregnant women with iodine deficiency based on regional experiences in the context of lacking national data. The study results suggest that the UK is iodine-deficient, according to WHO definition of iodine deficiency. This surprising result is of 'potential major public health importance' as stated by the authors. An accompanying editorial reminded us that in many Western settings diet has long been 'accidentally' fortified due to the use of iodine in dairy cattle husbandry – but unfortunately those practices are now changing! Urgent systematic studies on iodine status in all age groups are needed together with plans for improving iodine uptake in the general population.

Deletion of the RNaseIII enzyme Dicer in thyroid follicular cells causes hypothyroidism with signs of neoplastic alterations

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Background: Micro-RNAs (miRNAs) are small non-coding RNAs that regulate gene expression at mRNA posttranscriptional level. Functional maturation of most miRNAs requires processing of the primary transcript by Dicer, an RNaseIII-type enzyme. To date, the role of Dicer for normal miRNA processing and physiological organogenesis has been demonstrated by tissue-specific Dicer inactivation in several mouse models. The aim of this study was to investigate the role of Dicer for thyroid development and differentiation.

Methods: The authors generated mouse models in which Dicer expression has been inactivated at onset of thyroid development at the thyroid bud stage (embryonic day 8.5) and at the onset of thyroid functional and structural differentiation (embryonic day 14.5) in thyroid follicular cells.

Results: The early stages of thyroid organogenesis, preceding folliculogenesis, were unaffected by the loss of Dicer, presenting a normal bilobed thyroid gland in place. However, Dicer mutant mice were severely hypothyroid and died soon after weaning unless they were substituted with T₄. Tissue architecture was disturbed in Dicer knockout mice showing follicular disorganization and a strong downregulation of Nis expression. With increasing age, the thyroid tissue showed characteristics of neoplastic alterations as suggested by a marked proliferation of follicular cells and an ongoing dedifferentiation in the center of the thyroid gland, with a loss of Pax8, FoxE1, Nis and Tpo expression.

Conclusions: These data showed that loss of miRNA maturation due to Dicer inactivation results in severely disordered functional and structural thyroid differentiation.

The microRNA-processing enzyme Dicer is essential for thyroid function

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Background: Dicer is a type III ribonuclease required for the biogenesis of microRNAs (miRNAs), a class of small non-coding RNAs. MiRNAs regulate gene expression at the posttranscriptional level.

Methods: A thyroid follicular cell (TFC)-specific Dicer conditional knockout mice was generated by the authors to investigate the functional role of Dicer and miRNAs for normal thyroid development and TFC function.

Results: The authors showed that thyroid organogenesis and early TFC differentiation were not affected by Dicer inactivation. However, severe hypothyroidism gradually developed after birth, leading to reduced body weight and shortened lifespan. Histological and molecular analyses of knockout mice revealed a dramatic loss of the thyroid gland follicular architecture associated with functional aberrations and downregulation of several TFC differentiation markers.

Conclusions: The presented data showed that an intact miRNAs processing machinery is essential for normal function of the thyroid, and indicate that deregulation of specific miRNAs could be involved in human thyroid dysfunctions.

With this 'double pack' of evidence for the role of miRNAs for thyroid function, a new mechanism of thyroid physiology has been convincingly established. Both groups used the same approach of thyrocyte-specific conditional Dicer inactivation to disrupt functional maturation of miRNAs from the onset of thyroid development on. Rodriguez et al. added a second mouse model with 'late' Dicer inactivation at onset of thyroid differentiation, providing identical results as 'early' inactivation.

While the central aspect of postnatal loss of tissue architecture and secretory function due to loss of gene expression of differentiation markers at 1 month of life is shown by both groups, further analyses are complementary: Frezetti et al. documented in detail the thyroid differentiation at embryonic day 15.5, while Rodriguez et al. showed a highly increased proliferation rate in 4-week-old mice in both of their knockout mice strains. In conclusion, as thyroid organogenesis and initial thyroid differentiation is normal in Dicer knockout mice, miRNAs seem to be mandatory for maintaining thyrocyte function and thyroid structure.

Thyroid stem cells: surely more to come

Efficient derivation of purified lung and thyroid progenitors from embryonic stem cells

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Background: Nkx2-1 (NK2 homeobox 1, alternatively thyroid transcription factor 1) is a homeodomain-containing transcription factor expressed in lung, thyroid and brain. Two populations of Nkx2-1-expressing progenitor cells in the developing foregut endoderm give rise to the entire postnatal lung and thyroid epithelium. The aim of the study was to purify and characterize endodermal Nkx2-1-positive pneumocyte and thyrocyte precursors.

Methods: Embryonic stem cell culture and directed differentiation was performed by use of stage-specific selective inhibition and induction of key pathways.

Results: Efficient purification and directed differentiation of primordial lung and thyroid progenitors derived from mouse embryonic stem cells (ESCs) was realized in vitro by inhibition of TGF- β and BMP signaling, followed by combinatorial stimulation of BMP and FGF signaling. By use of an Nkx2-1(GFP) knock-in reporter, these progenitors were purified for expansion in culture. Transcriptome analyses revealed overlap of in ESC-derived Nkx2-1-positive cells with developing lung epithelium. Upon induction, they expressed a broad repertoire of markers indicative of lung and thyroid lineages.

Conclusions: The authors derived a pure population of Nkx2-1-expressing progenitors able to recapitulate the developmental milestones of lung/thyroid development.

Specific murine knockout models allowed dissecting the roles of different transcription factors and pathways for thyroid development during the last decade. However, up to now, knowledge on directed differentiation from pluripotent embryonic stem cells to specified thyrocyte progenitors was scarce. Longmire et al. were interested in the most proximal endodermal lineages, as thyroid and lung epithelia, and established in an elegant way a protocol of stepwise directed differentiation of embryonic stem cells to definitive endodermal progenitors (Foxa2+), lung/thyroid competent definitive endodermal progenitors (Foxa2+/Foxa3–), and Nkx2-1+ lung/thyroid progenitors, which finally expressed lung- or thyroid-specific differentiation markers. This technique overcomes the inability to access the very rare lung and thyroid progenitors within the developing endoderm and will allow studying early molecular events of thyroid specification and development.

Small-molecule MAPK inhibitors restore radioiodine incorporation in mouse thyroid cancers with conditional BRAF activation

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Background: Advanced human thyroid cancers, particularly those that are refractory to treatment with radioiodine (RAI), have a high prevalence of BRAF (v-raf murine sarcoma viral oncogene homolog B₁) mutations. The aim of the study was to evaluate the dependence of cancer biology BRAF expression.

Methods: The authors generated mice expressing the most commonly detected BRAF mutation in human papillary thyroid carcinomas (BRAF(V600E)) in thyroid follicular cells in a doxycycline-inducible (dox-inducible) manner.

Results: Dox induction of BRAF(V600E) induced highly penetrant and poorly differentiated thyroid tumors with abolished thyroid-specific gene expression and RAI incorporation. Discontinuation of dox extinguished BRAF(V600E) expression and re-established thyroid follicular architecture and normal thyroid histology. Treatment of mice with these thyroid cancers with small molecule inhibitors of either MEK or mutant BRAF reduced their proliferative index and partially restored thyroid-specific gene expression. Strikingly, treatment with the MAPK pathway inhibitors rendered the tumor cells susceptible to a therapeutic dose of RAI.

Conclusions: Thyroid tumors carrying BRAF(V600E) mutations are exquisitely dependent on the oncoprotein for viability. Genetic or pharmacological inhibition of its expression or activity is associated with tumor regression and restoration of RAI uptake in vivo in mice.

BRAF mutations are associated with aggressive and radioiodine uptake-resistant thyroid carcinomas. The authors established a genetically reversible in vivo mouse model of BRAF mutation-dependent thyroid carcinogenesis to answer two questions: (1) How dependent are the dedifferentiated thyrocytes from ongoing BRAF mutation expression? (2) Is it possible by pharmacological means to inhibit the oncogenic potential of BRAF mutations? In analogy with reversible activation of oncogenes, such as MYC in hematopoietic cell lines, the authors demonstrated the high dependence of dedifferentiated thyroid follicular cells in vivo on the permanent effect of the oncogenic BRAF mutation for maintenance of the cancer phenotype [14]. Further, they were able to reverse biological consequences of oncogenic BRAF activation by two different MAPK-signaling pathway inhibitors. More precisely, as a consequence of sodium/iodide symporter (NIS) re-expression at the basolateral membrane, radioiodine uptake was restored to an extent that tumor cells were rendered susceptible to therapeutic doses of radioiodine. These promising results open new avenues for the treatment of human thyroid cancer.

Important for clinical practice: thyroid nodules in children

Predictive factors of malignancy in pediatric thyroid nodules

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Surgery 2011;150:1228–1233

Background: According to the literature, thyroid nodules in children are more frequently malignant than in adult patients. The aim of the study was to identify clinical factors that may predict malignancy in pediatric thyroid nodules.

Methods: A retrospective analysis of 207 pediatric patients who underwent thyroidectomy for thyroid nodules was conducted over 15 years at two tertiary hospitals. Analyses examined predictive values of 16 clinicopathologic factors associated with cancer. Positive predictive values (PPVs) of fine-needle aspiration biopsy specimens (FNABs) were analyzed independently.

Results: Malignant thyroid histology was found in 41% of patients. Malignancy was more likely with family history of thyroid cancer (34.2 vs. 17.7%; $p = 0.111$), palpable lymphadenopathy (34.2 vs. 2.9%; $p = 0.001$), and hypoechoic nodules (52.2 vs. 19.2%; $p = 0.016$). Palpable lymphadenopathy indicated greater than 2-fold increased risk for malignancy (relative risk 2.18; 95% confidence interval 1.56–3.05). PPVs of FNAB results were 0.94 for malignancy, 0.63 for suspicious for malignancy, and 0.55 for indeterminate lesions. PPV for benign FNAB to be benign on final pathology was 0.71.

Conclusions: The authors concluded that malignancy was associated with family history of thyroid cancer and hypoechogenic lesions on ultrasonography; palpable lymphadenopathy had the greatest risk for malignancy. Further, a benign FNAB in children was not as accurate as in adults and the likelihood that an indeterminate nodule showed malignant histology was greater.

The 2009 revised American Association (ATA) guidelines for patients with thyroid nodules and differentiated thyroid cancer recommend that fine-needle aspiration biopsies should also be performed in children with thyroid nodules as in adults [15]. The aim of the study was first to identify clinical, radiological and pathological parameters which are associated with malignancy in the pediatric age group, and second to review the positive predictive value of fine-needle aspiration biopsies in their cohort. The study is of interest as it described a higher percentage of malignant thyroid nodules compared to earlier data, and found a relatively low positive predictive value of a benign fine-needle aspiration biopsy result in children. In summary, the authors conclude that the presence of the three identified clinical risk factors for malignancy should 'heighten suspicion for malignancy, even in the setting of a benign fine-needle aspiration biopsy, and certainly with an indeterminate biopsy'.

Chemotherapy and thyroid cancer risk: a report from the childhood cancer survivor study

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Background: The thyroid gland is one of the most radiosensitive organs. Childhood cancer survivors treated with radiation are at elevated risk for thyroid cancer. However, the effect of chemotherapy alone and in combination with radiotherapy on thyroid cancer risk is unclear. The objective of this study was to evaluate the chemotherapy-related risk of thyroid cancer in childhood cancer survivors and the possible joint effects of chemotherapy and radiotherapy.

Methods: The Childhood Cancer Survival Study is the largest cohort study to date with detailed treatment-related information including 12,547 5-year survivors of childhood cancer diagnosed during 1970 through 1986. Chemotherapy and radiotherapy information was obtained from medical records, and radiation dose was estimated to the thyroid gland. Cumulative incidence and relative risks were calculated with lifetable methods and Poisson regression. Chemotherapy-related risks were analyzed separately in a radiation dose-dependent manner.

Results: Histologically confirmed thyroid cancer occurred in 119 patients. 30 years after the first childhood cancer treatment, the cumulative incidence of thyroid cancer was 1.3% (95% CI 1.0–1.6) for females and 0.6% (0.4–0.8) for males. Among patients with thyroid radiation doses of ≤ 20 Gy, treatment with alkylating agents was associated with a significant 2.4-fold increased risk of thyroid cancer (95% CI 1.3–4.5; $p = 0.002$). Chemotherapy risks decreased as radiation dose increased, with a significant decrease for patients treated with alkylating agents ($p_{\text{trend}} = 0.03$). No chemotherapy-related risk was evident for thyroid radiation doses more than 20 Gy.

Conclusions: Chemotherapy with alkylating agents increased thyroid cancer risk only if the radiation dose was < 20 Gy.

Until now, most studies were unable to identify a significant association of chemotherapy and the risk of thyroid cancer as a second malignancy in childhood cancer survivors. New insights into thyroid cancer risk in this patient group come from the large Childhood Cancer Survival Study (CCSS). In a recent cohort analysis the authors observed a weak association of chemotherapy with thyroid cancer after adjustment for radiotherapy [16]. In the present study, they evaluated the possible joint effect of chemotherapy and radiation on thyroid cancer. They observed an increased risk for thyroid cancer in patients treated with alkylating agents. However, this effect was only significant with a radiation dose <20 Gy, in accordance with the fact that high radiation doses result in cell killing, while in the lower radiation dose range cell-sparing predominates. Although lower than the effect of radiation, chemotherapeutic agents may increase the risk of thyroid cancer in pediatric cancer survivors.

Reviews of interest for the pediatric endocrinologist

The following three extensive guidelines and reviews focus on common thyroid diseases and provide the current state of knowledge for these clinical problems for the adult but also for the pediatric age group.

Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum

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Thyroid 2011;21:1081–1125

Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists

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Treatment of differentiated thyroid cancer in children: emphasis on surgical approach and radioactive iodine therapy

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References

1. Henrichs J, Bongers-Schokking JJ, Schenk JJ, et al: Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the generation R study. *J Clin Endocrinol Metab* 2010;95:4227–4234.
2. Calvo RM, Jauniaux E, Gulbis B, et al: Fetal tissues are exposed to biologically relevant free thyroxine concentrations during early phases of development. *J Clin Endocrinol Metab* 2002;87:1768–1777.
3. Santiago-Fernandez P, Torres-Barahona R, Muela-Martinez JA, et al: Intelligence quotient and iodine intake: a cross-sectional study in children. *J Clin Endocrinol Metab* 2004;89:3851–3857.

4. Haddow JE, Palomaki GE, Allan WC, et al: Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 1999;341:549–555.
5. Kaguelidou F, Alberti C, Castanet M, Guitteny MA, Czernichow P, Leger J: Predictors of autoimmune hyperthyroidism relapse in children after discontinuation of antithyroid drug treatment. *J Clin Endocrinol Metab* 2008;93:3817–3826.
6. Mengreli C, Kanaka-Gantenbein C, Girginoudis P, et al: Screening for congenital hypothyroidism: the significance of threshold limit in false-negative results. *J Clin Endocrinol Metab* 2010;95:4283–4290.
7. Corbetta C, Weber G, Cortinovis F, et al: A 7-year experience with low blood TSH cutoff levels for neonatal screening reveals an unsuspected frequency of congenital hypothyroidism. *Clin Endocrinol (Oxf)* 2009;71:739–945.
8. Hertzberg V, Mei J, Therrell BL: Effect of laboratory practices on the incidence rate of congenital hypothyroidism. *Pediatrics* 2010;125(suppl 2):S48–53.
9. Li J, Pan P, Huang R, Shang H: A meta-analysis of voxel-based morphometry studies of white matter volume alterations in Alzheimer's disease. *Neurosci Biobehav Rev* 2012;36:757–763.
10. Dubuis JM, Glorieux J, Richer F, Deal CL, Dussault JH, Van Vliet G: Outcome of severe congenital hypothyroidism: closing the developmental gap with early high-dose levothyroxine treatment. *J Clin Endocrinol Metab* 1996;81:222–227.
11. Leger J, Ecosse E, Roussey M, Lanoe JL, Larroque B: Subtle health impairment and socioeducational attainment in young adult patients with congenital hypothyroidism diagnosed by neonatal screening: a longitudinal population-based cohort study. *J Clin Endocrinol Metab* 2011;96:1771–1782.
12. Narumi S, Muroya K, Abe Y, et al: TSHR mutations as a cause of congenital hypothyroidism in Japan: a population-based genetic epidemiology study. *J Clin Endocrinol Metab* 2009;94:1317–1323.
13. Mulrine HM, Skeaff SA, Ferguson EL, Gray AR, Valeix P: Breast-milk iodine concentration declines over the first 6 months' postpartum in iodine-deficient women. *Am J Clin Nutr* 2010;92:849–856.
14. Felsner DW, Bishop JM: Reversible tumorigenesis by MYC in hematopoietic lineages. *Mol Cell* 1999;4:199–207.
15. Cooper DS, Doherty GM, Haugen BR, et al: Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009;19:1167–1214.
16. Bhatti P, Veiga LH, Ronckers CM, et al: Risk of second primary thyroid cancer after radiotherapy for a childhood cancer in a large cohort study: an update from the childhood cancer survivor study. *Radiat Res* 2010;174:741–752.