Thyroid

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To select the relevant new clinical and fundamental data in the field of pediatric thyroidology is the yearly challenge when preparing the *Yearbook* chapter. The broad spectrum of the field ranges from maternal thyroid disorders during pregnancy, congenital hypothyroidism, autoimmune thyroid disease, iodine deficiency, rare disorders of thyroid hormone transport, cell membrane transport, metabolism and action, to thyroid cancer. It is not difficult to find fascinating papers – but it is a piece of work to crystalize the world's yearly production in thyroid research to a focused chapter. We hope you enjoy reading our selection of thyroid papers relevant to your clinical work and experimental research.

Consensus guidelines for congenital hypothyroidism

European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism

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Background: The aim was to formulate practice guidelines for the diagnosis and management of congenital hypothyroidism (CH).

Methods: A systematic literature search was conducted to identify key articles relating to the screening, diagnosis, and management of CH. The evidence-based guidelines were developed with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, describing both the strength of recommendations and the quality of evidence. In the absence of sufficient evidence, conclusions were based on expert opinion. Thirty-two participants drawn from the European Society for Paediatric Endocrinology and five other major scientific societies in the field of pediatric endocrinology were allocated to working groups with assigned topics and specific questions. Each group searched the literature, evaluated the evidence, and developed a draft document. These papers were debated and finalized by each group before presentation to the full assembly for further discussion and agreement.

Recommendations: The recommendations include: worldwide neonatal screening, approaches to assess the cause (including genotyping) and the severity of the disorder, the immediate initiation of appropriate L-T₄ supplementation and frequent monitoring to ensure dose adjustments to keep thyroid hormone levels in the target ranges, a trial of treatment in patients with suspected transient CH, regular assessments of developmental and neurosensory functions, consulting health professionals as appropriate, and education about CH. The harmonization of diagnosis, management, and routine health surveil

lance would not only optimize patient outcomes, but should also facilitate epidemiological studies of the disorder. Individuals with CH require monitoring throughout their lives, particularly during early childhood and pregnancy.

These guidelines aimed to summarize all available evidence to define recommendations for clinical management of congenital hypothyroidism covering neonatal screening, diagnosis, treatment, long-term outcome, genetic counseling and testing. It represents an important basis for all questions encountered in the context of caring for patients and families with congenital hypothyroidism. Please read it.

Late consequences

Cognitive development in congenital hypothyroidism: Is overtreatment a greater threat than undertreatment?

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Background: There is a fair body of literature reporting that undertreatment in children with congenital hypothyroidism (CHT) negatively affects their cognitive development; however only a few studies have investigated the effect of an overtreatment in this context. The authors aimed to evaluate whether early undertreatment (UT) and overtreatment (OT) influence cognitive development of children at age of 11 years.

Methods: 61 patients (27 with severe CHT, 34 with mild CHT) were tested at ages 1.8 years (Mental Development Index), 6 (Intelligence Quotient, IQ) and 11 years (IQ). Free T₄ concentration below or above the individual FT₄ steady-state concentration range (± 2 SD) was used to define UT and OT. Cognitive development scores were related to initial levels of TSH normalization and total duration of UT or OT episodes during the first 2 years of life. Control groups of healthy children were also tested at different ages (1.8, 6 and 11 years) and compared with CH patients.

Results: Patients with fast and moderate TSH normalization had 14.2 and 7.7 points higher Mental Development Index scores than patients with slow TSH normalization ($p = 0.001$). TSH normalization had no significant effect on IQ11. Patients with long and short overtreatment had IQ11s that were -17.8 and -13.4 points lower, respectively, than the IQ11s of patients with no overtreatment ($p = 0.014$). UT without OT was associated with normal development scores, but UT with OT was associated with -14.7 points lower IQ11s than UT without OT ($p = 0.005$).

Conclusions: These data suggest that CHT overtreatment during the first 2 years leads to lowered cognitive outcomes at 11 years, whereas undertreatment, if not complicated by overtreatment, results in a normal cognitive development. Fast TSH normalization at initial treatment leads to above-normal development scores at a young age but does not affect IQ at age 11 years.

This follow-up study on neurocognitive outcomes in children with congenital hypothyroidism evaluated the risks and benefits of levothyroxine overtreatment during the first 2 years of life in a long-term perspective. In a previous report of this cohort at 6 years of life [1], the authors found higher IQ scores in those who were overtreated (based on TSH suppression) during the first 5 years of life.

Two aspects are interesting. First, in contrast to their previous report, the authors defined under- and overtreatment not according to general reference values, but based on calculated TSH and FT₄ steady-state concentrations for each individual. Individual steady-state concentrations represented the mean value of a series of determinations under the most euthyroid conditions possible during follow-up of the patients, a new concept, published by the same authors recently [2]. They further showed that FT₄ values were more useful to define euthyroidism and to detect under- or overtreatment than TSH values. Second, the data presented suggest that early hypothyroidism might not be as harmful as previously thought, while overtreatment had more negative effects on neurocognitive

outcome at 11 years of age. This prospective study supports the consensus of ESPE on congenital hypothyroidism (see first manuscript in this chapter), which recommends to avoid overtreatment in CH patients. We await with interest the final analysis of this cohort to have an estimate on risks and benefits of overtreatment in patients with congenital hypothyroidism.

Factors associated with hearing impairment in patients with congenital hypothyroidism treated since the neonatal period: a national population-based study

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Background: Untreated hypothyroidism has long been recognized as a cause of hearing loss. However, only few studies have focused on patients with congenital hypothyroidism (CH) treated early since the inauguration of screening programs. The authors aimed to (i) characterize hearing impairment in a large cohort and (ii) determine if there is a relationship between hearing loss and disease severity and treatment quality.

Methods: Hearing was initially evaluated by self-reported questionnaires in 1,202 of the 1,748 eligible patients with CH of a large French cohort, who had already completed a questionnaire on health status at a median age of 23.4 years. Of 1,202 patients, 111 reported hearing impairment. For the characterization of the hearing impairment, a second questionnaire was sent to this group of patients in 2010–2011. Audiograms were obtained for one third of the patients (37 of 107) declaring hearing loss in this second questionnaire.

Results: Patients with CH had a risk of self-declared hearing loss more than 3 times higher than that of the reference population (relative risk (RR) 3.7, confidence interval (CI) 2.9–4.7). Risk factors for hearing loss later in life were: (i) the type of CH (higher in patients with athyreosis and gland in situ compared to those with thyroid ectopy, RR 2.61, CI 1.77–3.88), (ii) disease severity, evaluated by bone maturation delay at diagnosis (RR 2.29, CI 1.39–3.79), and (iii) other chronic diseases (RR 3.64, CI 2.35–5.62). There was a trend for association with low serum free T₄ levels (<5.0 pmol/l) at diagnosis (RR 1.47, CI 0.96–2.23). Median age at diagnosis of hearing impairment was 7 years (3.4–19). Hearing loss was mostly bilateral (90%), mild to moderate (96%), of sensorineural type (76%) and concerned high or very high frequencies (>1,000 Hz).

Conclusions: The authors showed that late-onset and progressive hearing loss still remains a problem and should always be considered in CH. They recommend a regular evaluation of hearing function, in order to improve the long-term prognosis and comorbidities in these patients.

This large nationwide French observational population study shows that hearing impairment is much more frequent in patients with CH than the general population (9.5 vs. 2.5%). Hearing loss is mostly of sensorineural type and the responsible mechanism involves the role of thyroid hormones in the maturation of sensory epithelium of inner ear and cochlea, explaining thus the relation with the disease severity. Middle ear defects may also be involved and explain the mixed or conductive deafness found in some patients. The authors insist on the assessment of hearing function later in infancy, as hearing loss cannot be detected by the screening methods currently available for testing in the neonatal period, with the exception of Pendred syndrome. Further, the authors suggest that hearing loss in patients with congenital hypothyroidism might be progressive after birth to become severe enough to be diagnosed only in early childhood. As a consequence, longitudinal studies assessing the hearing impairment in association with the thyroid status and the different fluctuations of hearing function should be realized in order to better understand the natural course of hearing impairment in CH.

Direct iodine supplementation of infants versus supplementation of their breastfeeding mothers: a double-blind, randomized, placebo-controlled trial

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Background: Iodine deficiency in infants can damage the developing brain. Currently, oral iodized oil is recommended to breastfeeding mothers to correct iodine deficiency in infancy when iodized salt is not available [3]. For non-breastfed infants or infants not receiving iodine-fortified food, direct supplementation should be given. However, there is little evidence for these recommendations. The authors aimed to compare safety and efficacy of direct versus indirect infant iodine supplementation.

Methods: A double-blind, randomized, placebo-controlled study (ClinicalTrials.gov, No. NCT01126125) was conducted in Morocco. Healthy breastfeeding mothers and their term newborn babies were block randomized by clinic day to receive either: one dose of 400 mg iodine to the mother and placebo to the infant (indirect infant supplementation), or one dose of about 100 mg iodine to the infant and placebo to the mother (direct infant supplementation). Primary outcome parameters were: maternal and infant urinary iodine concentrations, breast milk iodine concentration, maternal and infant thyroid-stimulating hormone (TSH) concentrations, maternal and infant thyroxine (T_4) concentrations, and infant growth. Outcome parameters were measured at 4 time points: baseline (0–8 weeks of age) and 3, 6, and 9 months. For statistical analysis, mixed effects models were used.

Results: The study included 241 mother-infant pairs. At baseline, median urinary iodine concentration was 35 $\mu\text{g/l}$ (IQR 29–40) in mothers and 73 $\mu\text{g/l}$ (29–237) in infants, confirming iodine deficiency: (1) As expected, maternal urinary iodine concentration ($p = 0.011$), breast milk iodine concentration ($p < 0.0001$), and infant urinary iodine concentration ($p = 0.042$) were higher in the indirect infant supplementation group than in the direct supplementation group. (2) Interestingly, maternal TSH ($p = 0.276$) and T_4 ($p = 0.074$) concentrations did not differ between the groups over the course of the study. (3) Infant TSH ($p = 0.597$) and T_4 ($p = 0.184$) concentrations were not significantly different. However, infants with thyroid hypofunction were more frequent ($p = 0.023$) in the direct supplementation group than the direct supplementation group. (4) The infant groups did not differ in growth measures, except that length-for-age z-score was higher in the directly supplemented infants ($p = 0.032$). (5) Finally, median infant urinary iodine concentration was sufficient ($>100 \mu\text{g/l}$) at 3 and 6 months of age in the indirect infant supplementation group versus only at 6 months in the direct supplementation group.

Conclusion: In moderate-to-severe iodine-deficient areas without effective salt iodization, one dose of 400 mg iodine as oral iodized oil given to the lactating mother soon after delivery can provide adequate iodine to their infants through breast milk for at least 6 months, enabling to protect the infants from iodine deficiency and hypothyroidism. Direct supplementation is less effective in improving infant iodine status.

Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC)

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Background: Iodine, a key component of thyroid hormones, is essential for fetal brain development. The UK has long been considered iodine replete. However, new data suggest mild iodine deficiency. In this study, the authors assessed whether mild iodine deficiency during early pregnancy was associated with an adverse effect on child cognitive development.

Methods: The authors included 1,040 mother-singleton child pairs from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort based on availability of (a) a urine sample from the first trimester (defined as ≤ 13 weeks' gestation; median 10 weeks (IQR 9–12)) and (b) a measure of intelligence quotient (IQ) in the offspring at age 8 years. Maternal first-trimester urinary iodine-to-creatinine ratios were categorized as <150 or >150 $\mu\text{g/g}$ according to WHO criteria for iodine deficiency in pregnancy. The association between maternal first-trimester iodine status and child IQ at age 8 years and reading ability at age 9 years was examined, including socioeconomic, parental, and child factors as confounders.

Results: Based on a median urinary iodine concentration of 91.1 $\mu\text{g/l}$ (IQR 53.8–143; iodine-to-creatinine ratio 110 $\mu\text{g/g}$, IQR 74–170) the complete cohort was classified as mildly-to-moderately iodine-deficient. After adjustment for confounders, children exposed to maternal first-trimester iodine deficiency (maternal urinary iodine <150 $\mu\text{g/g}$) were more likely to have scores in the lowest quartile for verbal IQ (odds ratio 1.58, 95% CI 1.09–2.30; $p = 0.02$), reading accuracy (1.69, 1.15–2.49; $p = 0.007$), and reading comprehension (1.54, 1.06–2.23; $p = 0.02$) than children of iodine-sufficient mothers in the first trimester. The association was strongest in children exposed to most severe iodine deficiency (maternal first-trimester urinary iodine <50 $\mu\text{g/g}$).

Conclusions: The data (1) confirms mild iodine deficiency in the UK and (2) re-emphasizes the importance of adequate iodine status during early gestation to prevent iodine deficiency-associated impairment of brain development. The authors conclude that iodine deficiency in pregnant women in the UK is an important public health issue that needs attention.

Iodine deficiency during pregnancy remains an important public health issue. This year, two new studies from Morocco and the United Kingdom elucidate further aspects of iodine deficiency during pregnancy.

The first paper by Bouhouch et al. describes a randomized placebo-controlled trial to compare the effect of iodine supplementation of lactating mothers ('indirect infant supplementation with 400 mg iodine') to iodine supplementation of their infants ('direct infant supplementation with 100 mg iodine') in a moderate-to-severe iodine-deficient region. Interestingly, infant urinary iodine concentrations were higher in the 'indirectly supplemented' infants versus 'directly supplemented' infants. Further, median urinary iodine levels were sufficient (>100 μg) at 3 and 6 months of age if the mother received 400 mg iodine compared to only at 6 months if the infants received 100 mg iodine. The route of supplementation had no influence on thyroid parameters of infants or mothers, but the number of infants with hypothyroidism was lower in the 'indirectly supplemented' group compared to the 'directly supplemented' group. In conclusion, iodine supplementation of breastfeeding mothers with a single dose of 400 mg iodized oil after delivery protects the infant from iodine deficiency for 6 months, while direct supplementation of the infant is less effective. It remains unanswered whether a higher dose of direct iodine supplementation (e.g. 200 mg) to infants would be more effective. This question is relevant for all infants who are not breastfed and needs urgent evaluation by randomized controlled studies.

The second paper by Bath et al. investigated in a large, prospective study the effect of mild-to-moderate iodine deficiency during pregnancy on cognitive outcome of the offspring at 8 years of age. Children exposed to iodine deficiency during the first trimester were more likely than unexposed children to be in the lowest quartile for verbal IQ, reading accuracy, and reading comprehension at 8 years of age. The subgroup of children exposed to more severe iodine deficiency had even lower scores than those with milder iodine deficiency. While the prospective, large-scale design is a strength of the study, the use of one single urinary iodine sample in the first trimester represents its major limitation due to the high intra-individual variability of urinary iodine values from day to day. Nevertheless, the study is important in the context of recent data from UK showing moderate iodine deficiency in schoolgirls aged 14–15 years in a cross-sectional study (described in our *Yearbook 2012* chapter) [4]. The study reinforces the need for active measures against even mild iodine deficiency in industrialized countries on the individual and society level.

Falling threshold for treatment of borderline elevated thyrotropin levels – balancing benefits and risks: evidence from a large community-based study

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Background: Over the last decade, a substantial increase in prescription of levothyroxine has been observed in the general population. The aim of the study was (1) to define the trend in TSH levels at the initiation of levothyroxine therapy and (2) to assess the risk of developing a suppressed TSH level during treatment.

Methods: The authors conducted a retrospective cohort study using data from the United Kingdom Clinical Practice Research Datalink. They identified 52,298 individuals who received a prescription for levothyroxine between January 1, 2001, and October 30, 2009. Main outcome measures were: median TSH level at levothyroxine prescription, odds of initiation of levothyroxine therapy at a TSH level ≤ 10.0 mIU/L, odds a low or suppressed TSH under levothyroxine substitution. Patients with (1) history of hyperthyroidism, pituitary disease, or thyroid surgery, (2) thyroid-altering medication, (3) levothyroxine prescription during pregnancy, and (4) lacking TSH level 3 months before the initiation of levothyroxine were excluded.

Results: The median TSH level at the initiation of levothyroxine therapy decreased from 8.7 to 7.9 mIU/L during the observational period. The odds ratio for prescribing levothyroxine at TSH ≤ 10.0 mIU/L in 2009 versus 2001 was 1.30 (95% CI 1.19–1.42; $p < 0.001$). Older individuals and individuals with cardiac risk factors had higher odds of initiation of levothyroxine therapy with a TSH ≤ 10.0 mIU/L. At 5 years after levothyroxine initiation, 5.8% of patients had a TSH of < 0.1 mIU/L. Depression or tiredness at baseline were associated with higher odds ratio for suppressed TSH, whereas cardiac risk factors (e.g. atrial fibrillation, diabetes mellitus, hypertension, and raised lipid levels) were not.

Conclusions: The authors observed (1) a decrease of the TSH level leading to initiation of levothyroxine treatment, and (2) a substantial risk of developing a suppressed thyrotropin level during therapy. They suggested large-scale prospective studies to assess the risk-benefit ratio of current treatment practice for subclinical hypothyroidism.

Treatment of subclinical hypothyroidism is recommended in adult patients to improve many aspects of health, e.g. depression, tiredness, etc. The presented retrospective cohort study of 52,000 patients provides evidence that subclinical hypothyroidism was treated more frequently in 2009 than in 2001 in the UK. Interestingly, 6% of patients showed suppressed TSH values after 5 years of treatment, especially patients with depression or tiredness. The limitations of the study include the absence of data on the prevalence of autoimmune thyroid disease (thyroid peroxidase antibodies) and a significant number lacking data 5 years after initial treatment.

The authors challenge the current practice by questioning the benefits of treatment of subclinical hypothyroidism and highlight the possible side effects, an issue that is relevant not only in adults but also in pediatric patients. Unfortunately, prospective studies evaluating the risk-benefit ratio of treating subclinical hypothyroidism are not on the horizon for children. Therefore, treatment of the individual patient should be initiated only after carefully weighing the benefits and risks, and should involve regular critical re-evaluation of the indication for therapy.

Thyroid hormone inactivation in gastrointestinal stromal tumors

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N Engl J Med 2014;370:1327–1334

Background: Consumptive hypothyroidism due to increased expression of iodothyronine deiodinase type 3 has been shown in infantile hemangiomas and vascular tumors.

Case Report: In this interesting case report, the authors identified severe consumptive hypothyroidism in a patient with a gastrointestinal stromal tumor (GIST) – analogous to consumptive hypothyroidism in infantile hemangioma – caused by marked overexpression of the thyroid hormone-inactivating enzyme type 3 iodothyronine deiodinase (D3) within the tumor. Affected patients, adults or children, require surveillance of thyroid hormone parameters and may require supernormal thyroid hormone supplementation.

Consumptive hypothyroidism due to paraneoplastic overexpression of the iodothyronine deiodinase type 3, which inactivates T_4 to rT_4 and T_3 to T_2 , results from a peripheral degradation of thyroid hormones exceeding the synthetic capacity of the thyroid gland. It was described a decade ago in large infantile hemangiomas [5]. The authors present for the first time a patient with a gastrointestinal stromal tumor suffering from consumptive hypothyroidism. It is noteworthy that, in contrast to patients with hemangiomas, patients with GIST are often treated with tyrosine kinase inhibitors which can themselves also cause hypothyroidism. So the take-home messages are: (1) watch out for tyrosine kinase inhibitor-induced hypothyroidism in oncology patients [6, 7] and (2) suspect consumptive hypothyroidism not only in infantile hemangiomas.

New concerns and new hope

Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the Generation R study

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Background: Premature delivery is associated with neonatal morbidity and mortality and psychiatric, metabolic, and cardiovascular disease later in life. The etiology of prematurity remains mostly unknown. Currently, conflicting data exist on the association of maternal thyroid function during pregnancy and risk of premature delivery. The authors analyzed the relation between maternal serum thyroid parameters and the risk of premature delivery in a large prospective population-based study (Generation R study).

Methods: Serum TSH, free T_4 (FT_4), T_4 , and TPO antibodies (TPOAbs) were determined during early pregnancy in 5,971 pregnant women. Further, information on gestational age at birth, maternal age, parity, smoking, socioeconomic status, ethnicity, maternal anthropometrics, and urinary iodine levels were available.

Results: Premature delivery (<37 weeks) occurred in 5.0% of all women. Spontaneous premature delivery was observed in 4.4% of the cohort. Very premature delivery (<34 weeks) was documented in 1.4%

of all births. Association with maternal serum thyroid parameters was as follows: (1) High TSH levels and subclinical hypothyroidism were associated with premature delivery but not with spontaneous premature delivery. (2) Maternal hypothyroxinemia was associated with a 2.5-fold increased risk of premature delivery, a 3.4-fold increased risk of spontaneous premature delivery, and a 3.6-fold increased risk of very premature delivery (all $p < 0.01$). (3) TPOAb positivity was associated with a 1.7-fold increased risk of premature delivery ($p = 0.01$), a 2.1-fold increased risk of spontaneous premature delivery ($p = 0.02$), and a 2.5-fold increased risk of very premature delivery ($p = 0.04$). These effects remained similar after correction for TSH and FT_4 levels.

Conclusions: In this prospective population-based study, hypothyroxinemia and TPOAb positivity were associated with an increased risk of premature delivery. In contrast to earlier studies, the increased risk in TPOAb-positive women seemed to be independent of thyroid function.

The authors of the Generation R study present new data on the effects of abnormal maternal thyroid parameters on pregnancy outcome in an iodine-sufficient population. They analyzed in a prospective population-based study the relation of TSH, T_4 and anti-TPO antibodies during early pregnancy on preterm delivery. Maternal hypothyroxinemia and anti-TPO antibodies were associated with higher risk for premature delivery, in contrast to TSH and subclinical hypothyroidism. The higher risk of preterm delivery with positive anti-TPO antibodies was in accordance with results from a meta-analysis, presented in *Yearbook 2011* [8].

The mechanisms behind these observations are not completely understood. However, the presence of anti-TPO antibodies probably reflects a generalized activation of the immune system and specifically a dysregulated activity of the immune system at the fetal-maternal interface. The mechanism by which maternal hypothyroxinemia could induce preterm delivery is also unclear. However, some authors suggest that lack of thyroid hormones might disturb placental histomorphology.

The presented data of this large, well-described, prospective population-based study are of interest, as several earlier studies with clearly smaller cohorts showed conflicting data on the association of hypothyroxinemia and preterm delivery in the last years.

Management of neonates born to women with Graves' disease: a cohort study

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Background: The authors aimed to evaluate the course of thyroid function and clinical outcomes during the first postnatal month in babies born to mothers with Graves' disease (GD).

Methods: This prospective observational study included 68 neonates born to mothers with GD. Three different groups were determined according to the thyrotropin receptor antibody (TRAb) status and anti-thyroid drug (ATD) status in the mother: a low-risk group for fetal thyroid dysfunction with negative TRAb assays and no ATD treatment (TRAb–/ATD–), $n = 27$, a group with positive TRAb assays and ATD treatment (TRAb+/ATD+), $n = 33$, and a third group with consistently negative TRAb assays but who received ATD treatment, $n = 8$. The neonates had a complete clinical examination, thyroid tests evaluation (TSH, free thyroxine (FT_4), free triiodothyronine (FT_3), TRAb), echocardiography, thyroid ultrasonography and bone maturation assessment.

Results: None of the neonates born to mothers with persistent TRAb-negative assays developed neonatal hyperthyroidism. Positive TRAb persisted and were present in cord blood assays of 24 among 33 neonates in the group TRAb+/ATD–. However, only 7 of them developed neonatal hyperthyroidism. Mean age at diagnosis was 5 days. Elevated FT_4 levels at day 3 and 7, but not at birth, predicted hyperthyroidism.

Conclusions: The authors showed that TRAb tests in mother during the third trimester of pregnancy and in the cord blood are predictive for the risk of neonatal hyperthyroidism. Another important predictive factor is FT_4 levels, which should be measured at birth and between days 3 and 5; FT_4 elevation (>35 pmol/l) during the first week of life is predictive of hyperthyroidism and warrants ATD treatment.

Graves' disease has an incidence of 55–80 cases/100,000 per year in women >30 years and 35–50 cases/100,000 per year in women 20–29 years old (see recommended review by Cooper and Laurberg below). Neonatal hyperthyroidism is a rare entity, with an estimated prevalence of 2% in offspring of mothers with Graves' disease, but with high mortality rates, up to 25% if not treated appropriately. Neonatal hyperthyroidism is usually not present at birth, but is clinically apparent from the end of the first week onwards. This study extends our knowledge about the measures to be taken in the context of babies born to mothers with Graves' disease as current guidelines do not propose a standardized procedure after birth [9, 10].

The aim of this study was to evaluate predictive factors for neonatal hyperthyroidism, in order to improve management of pregnant women with Graves' disease and postnatal monitoring of their newborns to diagnose neonatal hyperthyroidism before onset of severe clinical signs. Two known parameters were evaluated at different time points. Third-trimester and cord blood positivity for TRABs, and neonatal 3–5 day FT₄ values were predictive of neonatal thyrotoxicosis. Sensitivity of positive cord blood TRAb titers was 100%, but specificity was only 35%. It remains unknown why only 7/24 neonates with positive TRAb titers developed overt hyperthyroidism. Importantly, FT₄ values in cord blood were not predictive. Thus, positive TRAb titers define the subgroup of neonates who are at risk for neonatal hyperthyroidism and who need FT₄ monitoring during the first week of life. These data provide an approach to optimizing follow-up of neonates at risk of thyrotoxicosis.

Mechanism of the year

Embryonic exposure to excess thyroid hormone causes thyrotrope cell death

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Background: Central congenital hypothyroidism is more prevalent in children born to mothers suffering from hyperthyroidism during pregnancy. Based on this clinical observation, the authors hypothesized that thyroid hormone levels in utero would play a major role for the development of the hypothalamo-pituitary-thyroid axis.

Methods: The authors investigated the maturation of the hypothalamo-pituitary-thyroid axis during zebrafish development. They (1) characterized the ontogeny of negative feedback regulation of thyrotrope function and (2) examined the effect of excess thyroid hormone levels on thyrotrope development.

Results: First, the authors characterized the ontogeny of negative feedback regulation of thyrotrope function: Thyroid-stimulating hormone β subunit (*tshb*) and type 2 deiodinase (*dio2*) coexpression was found in zebrafish thyrotropes by 48 h after fertilization. Thyroid hormone mediated negative feedback regulation of *tshb* transcription appeared in the thyroid axis by 96 h after fertilization. Negative feedback regulation correlated with increased systemic thyroid hormone secretion from the developing thyroid follicles. Second, the authors examined the effect of excess thyroid hormone levels on thyrotrope development in a transgenic zebrafish that expresses GFP under the control of the *tshb* promoter to follow thyrotrope fates in vivo. They observed that early exposure to elevated thyroid hormone levels caused thyrotrope cell death. Thyrotrope numbers slowly recovered after removal of excess thyroid hormones.

Conclusions: Transient excess of thyroid hormones profoundly disturbed the thyrotrope population during a critical period of pituitary development. Such changes might impair functional reserve of thyroid-stimulating hormone (TSH) production and the TSH set-point later in life.

Although onset of fetal thyroid hormone synthesis starts at the end of the first trimester, the level of synthesis is low and steadily increases during the second trimester. Thus, the embryo and the fetus is

highly dependent on maternal thyroid hormones during this period. Regulation of thyroid hormone levels are fine-tuned by deiodinases, thyroid hormone transporters, and thyroid hormone receptors at the level of embryonic and fetal membranes and tissues. In parallel, maturation of the hypothalamic-pituitary-thyroid axis occurs characterized by functional negative feedback regulation by thyroid hormones.

In this elegant study, the authors use the zebrafish model to first characterize ontogeny of the hypothalamic-pituitary-thyroid axis and its negative feedback regulation by thyroid hormone. Second, they investigate the effects of increased thyroid hormone levels during early pituitary development. They provide evidence for long-term deregulation of the pituitary function by apoptosis of developing thyrotrope cells upon exposure to thyroid hormone excess during a developmental time window.

These fundamental data are not only fascinating on the molecular and developmental level but are relevant in the context of maternal hyperthyroidism, either due to maternal Graves' disease or due to overaggressive levothyroxine substitution of pregnant hypothyroid women in the first trimester.

Follow-up on a *Yearbook 2010* paper – genetics versus epigenetics

Role for tissue-dependent methylation differences in the expression of *FOXE1* in non-tumoral thyroid glands

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Background: Discordance between monozygotic twins for thyroid dysgenesis is a major argument for the involvement of epigenetic mechanisms in defects of thyroid gland development. The authors investigated whether differentially methylated regions (DMR) are present between human thyroids and matched leukocytes.

Methods: The authors used both genome-wide and candidate gene approaches: First, to compare the genome-wide methylation profile of thyroids and leukocytes, immunoprecipitated methylated DNA was interrogated on human promoter plus CpG island tiling arrays. Second, the methylation profile of the human *FOXE1*, *PAX8* and *NKX2.1* promoters were examined using bisulfite sequencing. Finally, the functional impact of CpG methylation of candidate gene promoters on gene expression was assessed with luciferase assays.

Results: First, neither genome-wide methylation profiling nor bisulfite sequencing of CpG islands of *PAX8* and *NKX2.1* promoters revealed DMRs between thyroid and leukocytes. However, by bisulfite sequencing of the *FOXE1* promoter, the authors revealed that the methylation level of two consecutive CpG dinucleotides (CpG₁₄ and CpG₁₅, not covered by the genome-wide methylation profiling) was significantly higher in leukocytes than in thyroid tissues, suggesting that methylation of this region may decrease *FOXE1* gene expression. Luciferase activities were decreased when *FOXE1* promoter constructs were methylated in vitro. Moreover, derepression of luciferase activity was observed when methylation of CpG₁₄ and CpG₁₅ was prevented by mutations.

Conclusion: The authors report a tissue-dependent DMR in the *FOXE1* promoter. This DMR contains two consecutive CpG dinucleotides which are epigenetic modifiers of *FOXE1* expression in non-tumoral tissues.

Promoter and CpG island methylation is an important mechanism of post-transcriptional regulation of gene expression. Based on discordance of monozygotic twins for thyroid dysgenesis, the authors suggested such epigenetic mechanisms as being involved in thyroid dysgenesis. In a first paper, reported in the *Yearbook* in 2010, Abu-Khudir et al. investigated three ectopic thyroid tissues versus eutopic thyroid tissues by transcriptome, methylome and genomic variation analysis [11]. Ectopic

thyroid tissue showed a different gene expression pattern than control tissue, but the expression profile was independent of the methylation status of gene promoters and CpG islands as it was for CNVs.

In this follow-up study, the authors searched for tissue-specific differentiated methylated regions by a genome-wide and a candidate gene approach in ectopic and eutopic thyroid tissues versus leukocytes. They found a differentially methylated region within the *FOXE1* gene promoter between leukocytes and thyroid, and showed by elegant functional assays that methylation of two CpG dinucleotides resulted in decreased *FOXE1* transcription. Thus, tissue-specific DNA methylation modified *FOXE1* expression adding new arguments for possible epigenetic regulation of gene expression during normal and pathologic thyroid development. Beside monogenetic forms of thyroid dysgenesis, epigenetic mechanisms are currently the most probable alternative cause of thyroid dysgenesis and we are waiting with interest for new data in this field.

Thyroid hormones and brain development – new concepts

Integrin $\alpha\beta3$ and thyroid hormones promote expansion of progenitors in embryonic neocortex

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Development 2014;141:795–806

Background: Neocortex expansion in the human is associated with the enlargement of the embryonic subventricular zone, which reflects an increased self-renewal and proliferation of basal progenitors. In contrast to humans, the vast majority of mouse basal progenitors lack self-renewal capacity. The integrin $\alpha\beta3$ receptor is the only known cell surface receptor for thyroid hormones. The authors hypothesized that the difference in embryonic neocortex progenitors between humans and rodents might be due to lack of a basal process contacting the basal lamina and downregulation of cell-autonomous production of extracellular matrix (ECM) constituents in an integrin $\alpha\beta3$ receptor-dependent manner.

Methods: The authors analyzed the effect of targeted activation of ECM receptor integrin $\alpha\beta3$ on basal neocortex progenitors in a transgenic mouse model.

Results: First, the authors showed that activation of integrin $\alpha\beta3$ promoted the expansion of basal neocortex progenitors by increasing cell cycle re-entry of Pax6-negative, Tbr2-positive intermediate progenitors, rather than basal radial glia, and a decrease in the proportion of intermediate progenitors committed to neurogenic division. Second, the authors observed, that tetrac, a thyroid hormone analog that inhibits the binding of thyroid hormones to integrin $\alpha\beta3$, completely abolishes the intermediate progenitor expansion observed upon targeted integrin $\alpha\beta3$ activation. This result suggested that expansion of basal neocortex progenitors required the binding of thyroid hormones to integrin $\alpha\beta3$.

Conclusion: Convergence of ECM and thyroid hormones on integrin $\alpha\beta3$ appeared to be crucial for cortical progenitor proliferation and self-renewal, and hence for normal brain development and the evolutionary expansion of the neocortex.

Transporters MCT8 and OATP1C1 maintain murine brain thyroid hormone homeostasis

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J Clin Invest 2014;124:1987–1999

Background: Allan-Herndon-Dudley syndrome (AHDS) is a severe form of psychomotor retardation characterized by high T_3 and low fT_4 and rT_3 levels. AHDS is linked to mutations in the thyroid hormone-specific monocarboxylate transporter *MCT8* gene. *Mct8* KO mice reproduce AHDS-associated thyroid

hormone abnormalities but do not exhibit neurological impairments as patients. While transport of the active form of TH (T_3) across the blood-brain barrier is strongly diminished in *Mct8* KO animals, pro-hormone (T_4) can still enter the brain, possibly due to the presence of T_4 -selective organic anion transporting polypeptide (OATP1C1).

Methods: The authors investigated mice deficient for both TH transporters, MCT8 and OATP1C1 (*Mct8/Oatp1c1* DKO).

Results: *Mct8/Oatp1c1* DKO mice showed similarly disordered peripheral thyroid hormone homeostasis compared to *Mct8* KO mice. In contrast to *Mct8* KO mice, not only T_3 but also T_4 uptake into the brains of *Mct8/Oatp1c1* DKO mice was strongly reduced. Evidence for CNS thyroid hormone deficiency of *Mct8/Oatp1c1* DKO mice included (1) highly decreased brain thyroid hormone content, (2) altered deiodinase activities and (3) disrupted thyroid hormone target gene expression. Consistent with delayed cerebellar development and reduced myelination, *Mct8/Oatp1c1* DKO mice displayed pronounced locomotor abnormalities.

Conclusions: Both thyroid hormone transporters Mct8 and Oatp1c1 are crucial for proper brain development and provide a basis to study the pathogenic mechanisms underlying AHDS.

These two studies provide important new insights into thyroid hormone action during brain development.

In an innovative study, Stenzel et al. show that thyroid hormones act not only via their nuclear thyroid hormone receptors α and β regulating gene expression in target cells, but also by binding to the cell membrane integrin $\alpha v \beta 3$ receptor mediating proliferation of neocortex progenitors. These results provide important new arguments for the concept of non-genomic effects of thyroid hormones in target cells during brain development.

The second study investigated the effect on brain development of combined inactivation of the so far best characterized thyroid hormone cell membrane transporters, Mct8 and Oatp1c1, in a double knockout murine model. The findings provide evidence for effects on multiple levels within the developing central nervous system. Further, this *Mct8/Oatp1c1* DKO mouse recapitulates the phenotype of human *MCT8* mutations with severe intracerebral thyroid hormone deficiency and disordered neuronal differentiation much closer than the *Mct8* KO mouse, providing a new model for pharmacological research for patients suffering from Allan-Herndon-Dudley syndrome due to *MCT8* mutations.

New concepts in genetics

Comprehensive genotyping and clinical characterization reveal 27 novel *NKX2-1* mutations and expand the phenotypic spectrum

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J Med Genet 2014;51:375–387

Background: The transcription factor *NKX2-1* is expressed in brain, lung and thyroid. Haploinsufficiency of *NKX2-1* causes a triad of benign hereditary chorea, interstitial lung disease and congenital hypothyroidism with a broad spectrum of phenotypes.

Methods: The *NKX2-1* gene was analyzed by Sanger sequencing in a cohort of patient with neurologic, lung or thyroid pathology. Moreover, CGH array was realized in patients negative for *NKX2-1* point mutations. EMSA was used to detect alterations of *NKX2-1* binding.

Results: In the cohort of 101 index patients, 17 point mutations and 10 deletions of *NKX2-1* were found. EMSA showed that DNA-binding capacity was not always affected by mutations in the homeodomain of *NKX2-1*. Two deletions did not encompass *NKX2-1* but led to a heterozygous loss of the 5'-neighboring gene *MBIP*, which encodes the MAP3K12-binding inhibitory protein. *Mbip* in situ

hybridization of early mice embryos revealed the same expression pattern as *NKX2-1* in brain, lung and thyroid. No mutation of *MBIP* was found in patients negative for *NKX2-1* mutation.

Conclusions: This study enlarged the phenotype of patients with *NKX2-1* mutations. The authors suggest expanding the screening of molecular defects in patients with brain-lung-thyroid syndrome to the whole genome.

This large-scale and very detailed study found 27 new *NKX2-1* gene defects and presents new clinical and molecular aspects of this syndromic form of congenital hypothyroidism. First, new associated clinical signs observed in this cohort were abnormal growth, congenital heart defects and fever episodes. Second, they investigated a possible role of the gene *MBIP* causing brain-lung-thyroid syndrome on the basis of 2 patients with deletions of *MBIP* but not *NKX2-1*. Developmental data showed coincidental expression of *Mbip* and *Nkx2-1* in the murine thyroid, brain and lung. However, a further 74 patients with no *NKX2-1* defects in this cohort were negative for mutations in the *MBIP* gene. Nevertheless, the approach to search for mutations outside the *NKX2-1* gene will provide new insights into the molecular basis of brain-lung thyroid syndrome, a disease occupying specialists not only in pediatric endocrinology, but also neonatology, pneumology, and neurology.

Identification of *PENDRIN* (*SLC26A4*) mutations in patients with congenital hypothyroidism and 'apparent' thyroid dysgenesis

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Background: Congenital hypothyroidism (CH) is the most frequent congenital endocrine disease. CH is caused by thyroid hormone biosynthesis defects in 15–20% and by thyroid dysgenesis in 80–85%. Genetic causes were identified in less than 10% of patients with thyroid dysgenesis.

Methods: In a consanguineous family with thyroid dysgenesis, whole exome sequencing was applied and results were validated by Sanger sequencing in a cohort of 94 patients with thyroid dysgenesis.

Results: The exome sequencing identified a homozygous missense mutation (p.Leu597Ser) in the *SLC26A4* gene of a patient with hypoplastic thyroid tissue without hypothyroidism and without deafness. This mutation was also found in 19 individuals in cohorts of hearing loss patients. The sequencing of the *SLC26A4* gene in the cohort of patients with thyroid dysgenesis identified another homozygous mutation p.Gln413Arg in a patient with congenital hypothyroidism, thyroid hypoplasia, deafness and mental retardation. This mutation has been described also as a compound heterozygous variant together with a heterozygous p.Val138Phe mutation in a patient with severe hearing problems. Both mutations were previously described as loss-of-function mutations in patients with Pendred syndrome and non-syndromic enlarged vestibular aqueduct. In the same cohort, heterozygous variants were found in 4 patients.

Conclusions: Mutations in *SLC26A4*, a gene known to cause thyroid dysmorphogenesis associated with deafness, were found by exome sequencing in patients with thyroid dysgenesis. The authors hypothesized a kind of secondary 'thyroid atrophy', rather than a primary defect of thyroid development in the sense of 'thyroid agenesis'. These results extend the variable clinical spectrum of patients with *SLC26A4* mutations.

It was expected that whole exome sequencing in patients with congenital hypothyroidism will provide new insights into molecular mechanisms of the disease. However, the authors themselves were probably surprised to identify a mutation in *Pendrin* (*SLC26A4*) in a patient presenting with congenital hypothyroidism with thyroid hypoplasia and without deafness. They screened a large cohort of patients and identified one further patient with a *SLC26A4* mutation with severe congenital hypothyroidism, thyroid hypoplasia and the typical enlargement of the vestibular aqueduct. The concept of secondary thyroid atrophy in patients with Pendred syndrome is new and interesting, but needs to be confirmed by serial thyroid measurements of thyroid size from birth in kindreds affected by Pendred syndrome. Whether this concept can be transferred to other forms of thyroid dysmorphogenesis will surely be clarified by further exome screening studies in patients with congenital hypothyroidism.

A novel *FOXE1* mutation (R73S) in Bamforth-Lazarus syndrome causing increased thyroidal gene expression

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Background: To date, five missense homozygous *FOXE1* mutations were found in patients with partial or complete Bamforth-Lazarus syndrome (congenital hypothyroidism with agenesis, cleft palate, spiky hair, with or without choanal atresia and bifid epiglottis). All disease-causing mutations in *FOXE1* have been reported as loss-of-function.

Methods: DNA of 8 patients with thyroid dysgenesis and cleft palate were sequenced for *FOXE1*. Mutations found were analyzed in vitro studies in transfected HEK293 cells and human primary thyrocytes, to validate the cause of the disease.

Results: One homozygous mutation of *FOXE1*, pR73S, located in the forkhead domain, was found in a patient with the complete Bamforth-Lazarus syndrome. Parents carrying heterozygous mutations were consanguineous and healthy. Unexpectedly, in vitro studies showed that the *FOXE1* mutation was a gain-of-function mutation by activating the promoters of *TG* and *TPO* in HEK293 cells and of *TG* in human primary thyrocytes.

Discussion: A gain-of-function *FOXE1* mutation was found in patients with classical Bamforth-Lazarus syndrome. Mutations of *FOXE1*, gain- or loss-of-function gave the same phenotype.

Mutations in the *FOXE1* gene represent the rarest monogenetic form of congenital hypothyroidism. In contrast to all other mutations reported so far, the authors identified and functionally tested a new *FOXE1* mutation that results in *gain-of-function*, but remarkably leads to the same phenotype as *loss-of-function* mutations. A fine regulation of this transcription factor during development seems to be essential to ensure normal thyroid and palate development.

Major steps forward in cancer genetics

Identification of kinase fusion oncogenes in post-Chernobyl radiation-induced thyroid cancers

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Background: Exposure to ionizing radiation during childhood markedly increases the risk of developing papillary thyroid cancer.

Methods: The authors analyzed thyroid tissues from 26 Ukrainian patients with thyroid cancer by RT-PCR of candidate genes, mass spectrometry, and next-generation RNA sequencing. The patients were selected according to the following criteria: (1) younger than 10 years of age and (2) living in contaminated areas during the time of the Chernobyl nuclear reactor accident.

Results: The authors identified non-overlapping somatic driver mutations in all 26 cases. 22 tumors (84%) harbored fusion oncogenes that arose primarily through intrachromosomal rearrangements. Altogether, 23 of the oncogenic drivers identified in this cohort aberrantly activate MAPK signaling, including the 2 somatic rearrangements resulting in fusion of transcription factor ETS variant 6 (*ETV6*) with neurotrophic tyrosine kinase receptor, type 3 (*NTRK3*) and fusion of acylglycerol kinase (*AGK*) with *BRAF*. Two other tumors harbored distinct fusions leading to overexpression of the nuclear receptor PPAR- γ . In a control group of children of the same geographical area but not exposed to radiation, these fusion oncogenes were less prevalent than in then radiation-exposed group of children.

Conclusions: Radiation-induced thyroid cancers harbor fusion oncogenes which commonly trigger the MAPK signaling pathway or, less frequently, a PPAR- γ -driven transcriptional program.

Sporadic papillary thyroid carcinomas display in about half of the cases point mutations in the serine/threonine kinase gene, *BRAF*, while gene rearrangements are less frequent. In contrast, in post-Chernobyl radiation associated papillary thyroid carcinoma, a high prevalence of gene rearrangements was observed (e.g. nuclear receptor co-activator 4-RET) with a low prevalence of *BRAF* point mutations.

This study adds to current knowledge the following aspects: (1) Radiation in a very homogenous pediatric cohort induced a selective increase of oncogenic gene rearrangements but not point mutations compared to an age- and geographically-matched control group. (2) The number of gene rearrangements in the tumors was not different between radiation-exposed and not-exposed children, suggesting that not the number but rather the nature of rearrangements are responsible for the biology of radiation-induced thyroid cancer. (3) Most of the gene rearrangements resulted in a constitutive activation of the MAPK signaling pathway. These results represent an important gain of knowledge on molecular mechanisms of radiation-induced thyroid carcinogenesis, and opening avenues for molecular pharmacological therapies.

Prevalence by age and predictors of medullary thyroid cancer in patients with lower risk germline RET proto-oncogene mutations

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Background: The tumor biology of hereditary medullary thyroid carcinoma (MTC) due to high-risk germline mutations in the *RET* gene is well characterized and the recommended age for prophylactic thyroidectomy in mutation carriers is clearly defined. In contrast, tumor biology of the less frequent lower-risk germline mutations is uncertain, and recommendations for age at thyroidectomy are less clear.

Methods: The authors gathered information on individual patients from an institutional database and by reviewing the literature. They included only patients with American Thyroid Association level A or B mutations (Mutations in codons (c) c533, c609, c611, c618, c620, c791, and c804 of the *RET* gene) and information on age at thyroidectomy, preoperative calcitonin level, and clinical outcome. Data were used to estimate the cumulative prevalence of MTC and/or assess likelihood of MTC stratified by codon.

Results: They report 503 patients without age limit (78 own patients and 425 published cases). 236 of 503 patients had MTC. Cumulative prevalence and median time to MTC varied by codon and within ATA risk levels ($p < 0.0001$). Patients harboring c620 mutations were 2.8–6.9 times more likely to have MTC than other level B mutation carriers, and 5.1–21.7 times more likely than level A mutation carriers. Cumulative prevalence of MTC by age 20 was 10% or lower for codons 533, 609, 611, 791, and 804. By age 50, it varied from 18% for codon 791 to 95% for codon 620. An elevated preoperative calcitonin level strongly predicted MTC on final pathology, though false negative rates varied by codon ($p < 0.0001$). Positive predictive values ranged from 76 to 100% by codon with an overall positive predictive value of 87% across codons.

Conclusions: The findings allow a more precise overview on tumor biology of the ATA level A and B risk *RET* germline mutations, supporting the concept of ‘codon-based’ management approaches coupled with clinical data such as calcitonin levels also in lower risk *RET* mutations.

This extensive study is of importance, as tumor biology of *RET* mutations other than the frequent high-risk mutation c634 is not clearly characterized and recommendations in the current ATA guidelines remain vague [12]. The results provide important information on estimated cumulative risk for medullary thyroid carcinoma for each codon and will certainly help to define more precise recommendations for the next updated guidelines for hereditary medullary thyroid carcinoma. In accordance with previous work in high-risk *RET* mutations, the predictive value of preoperative calcitonin levels for medullary thyroid carcinoma in lower-risk mutations were confirmed.

Classification and proposed nomenclature for inherited defects of thyroid hormone action, cell transport, and metabolism

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This statement by the key opinion leaders recommends a new classification and nomenclature of the following pathologies and diseases: (1) Thyroid hormone cell membrane transport defects (THCMTD) encompassing *MCT8* defects causing Allan-Herndon-Dudley syndrome and yet unidentified genetic defects in contrast to thyroid hormone transport defects due to serum transport protein disorders. (2) Thyroid hormone metabolism defects (THMD) such as *SBP2* defects and further yet unidentified genetic forms. (3) Thyroid hormone action defects (THAD), refining the widely used expression ‘resistance to thyroid hormone’ (RTH) to (i) resistance to thyroid hormone due to mutations in the thyroid hormone receptor β (RTH β), (ii) resistance to thyroid hormone without mutations in the thyroid hormone receptor β gene (noTR-RTH β), (iii) the recently described form of RTH α due to mutations in the thyroid hormone receptor α gene, (iv) hypersensitivity to thyroid hormones (yet without genetic defects identified), and finally (v) ‘other THADs’ not yet genetically characterized. This is a paper to be read by everyone who cares for patients with these diseases.

The Na^+/I^- symporter (NIS): mechanism and medical impact

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The sodium/iodide symporter (NIS) is the limiting step for onset of thyroid hormone synthesis in the human fetal thyroid and the molecular basis for diagnostic and therapeutic radioiodine uptake in the thyroid and in other NIS-expressing organs. This extensive review discusses all aspects of normal and disordered NIS function in congenital hypothyroidism (causing the rare iodide transport defect), thyroid cancer and the potential of *NIS* gene transfer for other cancer types. Everything you ever wanted to know about cellular iodine uptake.

Hypothyroidism in pregnancy

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Hyperthyroidism in pregnancy

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This double-pack of extensive literature reviews give a succinct overview on all problems encountered during hypo- or hyperthyroidism during pregnancy. As pediatric endocrinologists are more and more involved in discussions on individual patients in everyday clinics as well as in research projects, we believe that these two papers are a valuable basis for all the questions you may encounter in interdisciplinary discussions with obstetricians and adult endocrinologists.

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