Introduction

Thyroid disorders are still a cause of health concerns, major illness, and comorbidities in neonates, children and adolescents around the world. Neonatal screening programs involve testing for congenital hypothyroidism using thyroid stimulating hormone (TSH) measurements in dried blood spots, and in developed countries, it is clinically and ethically mandatory to install neonatal screening programs for hypothyroidism. Also, as far as obese children are concerned, families and doctors alike tend to automatically ask about a child’s thyroid status. In addition, fatigue in a schoolchild is frequently met with concerns about whether or not there was an underlying thyroid dysfunction. However, most of the time, common causes such as psychosomatic illness or normal exhaustion are the reason for tiredness and thyroid function in these children are quite normal.

Both hypothyroidism and hyperthyroidism may occur early in life, and thyroid cancer is of relevance in paediatric oncology and may be either sporadic or related to radiation exposure (Chernobyl accident and alike). However, overall clinically relevant disorders of the thyroid are still rather uncommon: congenital hypothyroidism occurs at a frequency of 1 in 3000, and acquired hypothyroidism in Hashimoto’s thyroiditis occurs in 1 in 2000 (1). Genetic analysis of primary congenital hypothyroidism has revealed that many genes are involved in the migration of the thyroid during development, organogenesis of the thyroid and also the development of (autoimmune) inflammation of the thyroid. In a comprehensive study involving 48 children with congenital hypothyroidism from Poland, Kumorowicz-Czoch et al. investigated the morphological and biochemical phenotype of the paired box transcription factor (PAX8) gene variants/mutations in hypothyroidism (6). Two novel heterozygous mutations in the PAX8 gene were discovered and functional analysis is under way to elucidate the mechanism leading to organ failure (6). Functional characterisation of a novel gene variant, p.S304R, in the hinge region of the TSH receptor that had been discovered in a child with congenital hypothyroidism was performed by Cerqueira et al. Surprisingly, this novel TSHR gene variant neither led to altered TSH binding to the mutated receptor nor to impaired cAMP signalling (7). This finding impressively shows that gene variants that are being discovered in patients with disorders still have to be tested as to their functional relevance. This fact has to be stressed again and again and is not only relevant for thyroid disease but is relevant to other congenital disorders as well.

Hypothyroidism

It is important to again note that congenital hypothyroidism occurs at a frequency of 1 in 3000, and acquired hypothyroidism in Hashimoto’s thyroiditis in 1 in 2000 (1). Genetic analysis of primary congenital hypothyroidism has revealed that many genes are involved in the migration of the thyroid during development, organogenesis of the thyroid and also the development of (autoimmune) inflammation of the thyroid. In a comprehensive study involving 48 children with congenital hypothyroidism from Poland, Kumorowicz-Czoch et al. investigated the morphological and biochemical phenotype of the paired box transcription factor (PAX8) gene variants/mutations in hypothyroidism (6). Two novel heterozygous mutations in the PAX8 gene were discovered and functional analysis is under way to elucidate the mechanism leading to organ failure (6). Functional characterisation of a novel gene variant, p.S304R, in the hinge region of the TSH receptor that had been discovered in a child with congenital hypothyroidism was performed by Cerqueira et al. Surprisingly, this novel TSHR gene variant neither led to altered TSH binding to the mutated receptor nor to impaired cAMP signalling (7). This finding impressively shows that gene variants that are being discovered in patients with disorders still have to be tested as to their functional relevance. This fact has to be stressed again and again and is not only relevant for thyroid disease but is relevant to other congenital disorders as well.

It is important to note that hypothyroidism may both mask other causes of fatigue, tiredness, or clinical signs of anaemia and may also be co-incidental with any of these. For example, in this issue of JPEM Bargenda et al. report...
on a 16-year-old girl who was admitted to hospital because of renal insufficiency in the course of chemotherapy for uterine cervical cancer. Erythropoietin failed to correct her anaemia, and subclinical hypothyroidism was diagnosed and subsequently treated. Upon normalisation of thyroid function, haemoglobin levels increased and the clinical situation improved (8). Despite the fact that this report seems to be unique and potentially clinical improvement upon thyroid supplementation might be coincidental, it stresses the fact that thyroid function should be tested in patients with complex disorders at least once if there is any suspicion of hypothyroidism or any clinical signs suggestive of thyroid dysfunction. Inflammatory markers and oxidative biomarkers were measured by Qiu et al. in 23 children with well-controlled congenital hypothyroidism. While it remains at the discretion of the authors why such surrogate markers were measured in the first place, it is interesting to note, that oxidative stress and inflammation might occur in children with hypothyroidism despite appropriate hormone replacement. Whether or not these findings will translate in contributing to clinical problems and may eventually lead to improved decision making remains unanswered (9). The last study on hypothyroidism in this issue of our journal investigates autoimmune diseases that accompany Hashimoto's thyroiditis in children and adolescents in Turkey. As is expected, of the 57 patients with Hashimoto's disease, 48 were female, and nine were male. Cardiac problems were frequent, and mitral valve problems were detected in 10 patients. In addition, antinuclear antibodies were measured in 15 cases and anti-cardiolipin IgG in two. An additional panel of autoantibodies was detected in the sera of the children with Hashimoto's, and this suggests an underlying general autoimmune disease or risk for other autoimmune disorders in these patients (10). Unfortunately, it remains unclear whether or not monitoring of autoantibody levels should be performed on a regular basis and importantly whether or not such monitoring would be of benefit for the patient and be of relevance in clinical decision making.

Hyperthyroidism

In paediatric patients, hyperthyroidism is much less frequent than hypothyroidism (1). Yet, hyperthyroidism may cause major diagnostic dilemmas and might even be overlooked, especially in children with other rare diseases. We are grateful to the authors who share their anxieties and thoughts when caring for children with severe chronic disease and wish to emphasise that hyperthyroidism due to Graves' disease is a rare disorder in children but must not be overlooked. Hyperthyroid storm in neonates is also rare and can be overlooked and misdiagnosed easily. Cao et al. report on a case of neonatal thyroid storm secondary to maternal Graves' disease and summarise diagnostic algorithms and treatment options of neonatal hyperthyroidism. We are grateful to the authors and also to the parents who allow us to see the clinical features of thyroid storm in this child and commend the therapeutic efforts and long-term care of the baby (11).

**Thyroid cancer and news about thyroid nodules**

Radiation accidents and environmental exposure have led to an increase of thyroid cancers in some regions of the world. In general, it is thought that the prognosis of young (paediatric) patients with differentiated thyroid cancer is better than that of older (adult) patients. The article by Bal et al. reports on 53 patients with thyroid cancer and pulmonary metastases who were aged <21 years and were followed for a median of 72 months. Of these patients from India, 38 became disease free. Older patients (>15 years), patients with macronodular pulmonary metastases, and those in whom less than total/near-total thyroidectomy had been performed had a reduced likelihood of remission. In order to design better treatment strategies for children and adolescents with thyroid cancer, it is important to know information on remission odds and factors which relate to prognosis (12).

Importantly, Arva et al. from the Chicago Northwestern University analysed data from 187 fine needle aspirate specimens from 180 patients with thyroid nodules to determine whether or not imaging techniques would help to better differentiate nodules that upon cytological investigation appeared atypical. Patients were on average 13.5 years old and the size of the nodules ranged from 0.4 to 5.5 cm. The authors propose to use a radiologic score based upon ultrasound examinations to reclassify atypical lesions and conclude that ultrasound of thyroid nodules can and should complement cytopathology findings in order to help clinicians and patients/families to decide the best treatment strategies when dealing with atypical thyroid nodules in children and adolescents (13).

**Conclusions**

In this issue of our journal, we have compiled comprehensive data on several aspects of thyroid disorders in
the neonatal period, childhood, and adolescence. We aim to highlight the importance of clinical signs of hyperthyroidism and some of the still challenging issues of hypothyroidism as well as try to add to our understanding of thyroid cancers in children and adolescents.

References


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