Editorial

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Thyroid – what is a healthy thyroid function test?

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Distinction between normal and hypo- and hyperthyroid states is sometimes and somewhat difficult due to the hitherto lack of normative data from large cohorts of healthy children across early age as well as due to the failure of many publications to clearly relate clinical symptoms to distinct biochemical features [1].

Recently, we have published reference data on thyroid function in healthy newborns, infants, children, and adolescents. We were able to establish age- and sex-specific reference intervals for serum concentrations of thyrotropin (TSH), free triiodothyronine (fT3), and free thyroxine (fT4) in a large cohort of healthy infants, children, and adolescents. Also, we have asked whether or not there was an association of TSH, fT3, and fT4 with sex, body mass index (BMI), and pubertal stage. In our study, 9,404 blood serum samples from 3,140 young individuals from birth to 18 years of age without thyroid affecting diseases were included. TSH, fT3, and fT4 serum concentrations were measured and age- and sex-specific reference ranges were established. To investigate the association of TSH, fT3, and fT4 with age, sex, weight status, and the role of puberty-based changes, the hormone levels and BMI values were converted to standard deviation scores (SDS). We have found that TSH, fT3, and fT4 were indeed age and sex dependent. Puberty was accompanied by decreased TSH, decreased fT3 with a temporary peak in males, and a temporary nadir of fT4 in Tanner stage 3 for both sexes. BMI-SDS was positively associated with TSH-SDS (β=0.081, $p<0.001$); the effect was more pronounced in overweight subjects (β=0.142, $p<0.01$) and insignificantly negative in underweight subjects (β=−0.047, $p>0.05$). BMI-SDS was positively associated with fT3-SDS (β=0.066, $p<0.001$) and negatively associated with fT4-SDS (β=−0.135, $p<0.001$), with the effect insignificantly less negative in overweight children (β=−0.055, $p>0.05$). In conclusion, age- and sex-specific reference intervals are important for the interpretation of measurements of TSH, fT3, and fT4 in children and adolescents. Importantly, factors such as BMI and puberty should be taken into consideration when using measurements of TSH and thyroid hormones to diagnose or monitor treatment of thyroid diseases [2].

For decades, discussions as to the existence and definition of subclinical hypothyroidism have been ongoing. Here, Metwalley et al. present a review article on subclinical hyperthyroidism: subclinical hyperthyroidism (SH) in their view is defined as serum thyroid-stimulating hormone (TSH) below the lower limit of the reference range in the presence of normal free T4 and free T3 levels. Depending on the degree of TSH suppression, subclinical hyperthyroidism was defined as mild (TSH, 0.1–0.45 mU/L) or severe (TSH<0.1 mU/L). Patients with low TSH but normal thyroid hormone levels are most often asymptomatic. However, when symptoms are present, they appear similar to the symptoms in patients with overt hyperthyroidism, although they are usually milder as would be expected. Whether or not this condition should be treated is uncertain; however, management should be individualized. As the authors point out, this review was put together after an extensive literature search and long-standing clinical experience of the authors [3].

Hyperthyroidism is usually part of an autoimmune disease most often due to anti-TSH receptor antibodies as in Graves' disease but can also occur in some hereditary disorders: in this issue of our journal, Rosinha et al. report on hyperthyroidism in McCune–Albright syndrome in a 13-year-old boy. It is very well known that McCune–Albright syndrome is rare and is mainly characterized by fibrous dysplasia, cutaneous hyperpigmentation, and importantly hyperfunctioning endocrinopathies. The patient presented with café-au-lait spots in the lumbosacral region and disabling polyostotic fibrous dysplasia. Bone disease required several surgical interventions and bisphosphonate treatment from the age of 3 years±9 months mainly due to persistent and severe pain. Clinical hyperthyroidism was discovered at 5 years and 1 month with a T3/T4 ratio greater than 20. Treatment with antithyroid drugs was carried out for 7 years. Interestingly, there was a progressive improvement in pain severity 8 months after starting antithyroid drugs, allowing treatment with pamidronate to be discontinued. Total thyroidectomy had to be performed at 12 years and 5 months. This case demonstrates the complexity and broad clinical

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spectrum of endocrine disease in McCune–Albright syndrome and points to the need for correcting all hyperfunctioning endocrine states before starting antiresorptive therapy, namely bisphosphonates [4].

As hyperthyroidism is relatively rare during childhood, thyroid storm is an even more uncommon but severe manifestations of hyperthyroidism. This endocrine emergency can be fatal if it is not recognized early as is extrapolated from adult data. In pediatrics, the current literature is limited to case reports and case series. Therefore, in another review article, available data in pediatric cases and case series of thyroid storm have been collected [5]. Studies included case reports and case series in English and Spanish from patients between the ages of 0 and 21 years with clinical features consistent with a diagnosis of thyroid storm based on American Thyroid Association (ATA) 2016 guidelines, published between 2000 and 2022 [5]. Data from 45 patients (mean age was 11.25 years) were found, with the most cases from Asia (26%). The most common clinical features were sinus tachycardia (86.7%) and fever (64%), followed by altered mental status (46%) and diarrhea (31%). Graves' disease was the most common cause, and infection the most common precipitant. Thirty-one percent of patients received treatment with four components; however, morbidity and mortality were not clinically significant with those who did not. The authors conclude that thyroid storm has a heterogeneous presentation with multisystemic signs. The most common symptoms of thyroid storm as reported in this review were fever, tachycardia, diarrhea, and altered mental state. Further studies may be needed to standardize the diagnosis and management of thyroid storm in children and assess how the delay in diagnosis of hyperthyroidism may impact prognosis in case patients developing thyroid storm [5].

Total thyroidectomy occasionally has to be performed in pediatric patients with thyroid cancer or with Graves' disease. Under these circumstances, transient hypocalcemia is a frequently occurring complication after pediatric total thyroidectomy, while permanent hypoparathyroidism (PH) is relatively uncommon. Unfortunately, there is no diagnostic algorithm to predict which patients will develop PH based on postoperative makers and which patients will not. In a study by Keane et al., the authors aimed to identify pediatric patients who are at high risk of PH following thyroidectomy based on 6 h postoperative parathyroid hormone (PTH) value. Authors performed a retrospective review of 122 pediatric patients undergoing total thyroidectomy between 2016 and 2022 at one institution. Outcome of interest was permanent hypoparathyroidism, defined as need for continuous calcium supplementation at 6 months postoperatively. Receiver operating characteristic (ROC) analysis was used to determine PTH value at 6 h postoperative that was predictive of permanent hypoparathyroidism. According to Keane et al., rates of permanent hypoparathyroidism were similar to those described in the literature with 12 patients (10.9%) developing PH. In patients who developed PH, mean 6 h postoperative PTH was 5.12 pg/mL. In contrast, mean 6 h postoperative PTH level in those who did not develop PH was 31.34 pg/mL ($p<0.0001$). The 6 h postoperative PTH value predictive for PH was 11.3 pg/mL. PTH cutoff of ≤11.3 pg/mL had a sensitivity of 100%, a specificity of 72.2%, a positive predictive value (PPV) of 27.0%, and a negative predictive value (NPV) of 100%. In conclusion, 6 h postoperative PTH values were found to be predictive of permanent hypoparathyroidism in pediatric total thyroidectomy in this study: in addition, and importantly, a 6 h postoperative PTH level of >11.3 pg/mL excluded permanent hypoparathyroidism, but when PTH was ≤11.3 pg/mL at 6 h, approximately 1/3 of patients may persist with permanent hypoparathyroidism [6].

In summary, clinical issues of thyroid function are frequent in pediatric practice, and most importantly pediatric patients with thyroid disease are often encountered in pediatric endocrinology clinics. Normative date of thyroid function have to be at hand when children with thyroid issues are being seen in the clinic. Congenital hypothyroidism, autoimmune hypothyroidism, and thyroid cancer as well as hyperthyroidism in Graves' disease have to be detected early and treated appropriately. Less frequently occurring thyroid disease may still pose diagnostic and therapeutic difficulties.

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