Editorial

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Congenital hypothyroidism

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The prevalence of hypothyroidism due to any cause is thought to range between 0.3 and 0.7% in the United States and between 0.2 and 5.3% in Europe. The differences in the reported prevalence and incidence are due to the differences in definitions that underlie the estimates. Hypothyroidism occurs frequently as an autoimmune disorder in combination with other autoimmune diseases such as type 1 diabetes, gastric atrophy, celiac disease and multiple autoimmune endocrinopathies. In addition, patients with Down syndrome or Turner syndrome also exhibit a higher prevalence of autoimmune thyroid disease. In later life, iodine deficiency can also be a leading cause of hypothyroidism. Importantly, there are numerous forms of congenital hypothyroidism (CH) with a large variety of underlying causes such as genetic mutations in iodine transporters, in the Pendrin gene, the thyroid-stimulating hormone (TSH) or TSH receptor and a number of transcription factors which are important for the development of the thyroid gland. Causes of CH also include a number of iodination defects. Clinical signs of hypothyroidism include dry skin, hair loss, impairment of renal function, constipation, neurological problems (developmental delay), intellectual disability and even psychiatric and cardiovascular symptoms. During childhood and adolescence, growth impairment and even growth arrest as well as overweight are also frequent and devastating sequelae of thyroid dysfunction [1–5].

In this issue of the journal, four articles have been assembled which report on the various aspects of CH. Follow-up of patients with CH is not always easy: for example, the initial dosing of levothyroxine in infants with congenital hypothyroidism may require frequent dose adjustments and both iatrogenic hyperthyroidism as well as hypothyroidism have been reported on follow-up. When the recommended starting doses of levothyroxine between 10 and 15 µg/kg are administered in the neonatal period, a sizable proportion of newborns treated at this higher end of the dosage range may become biochemically hyperthyroid at follow-up visits. Indeed, in the study by Craven and Frank [6], 104 patients included in the period between 2002 and 2012, the average starting dose

of levothyroxine was 12 ± 2.5 µg/kg and at follow-up 36.5% required a dose reduction because of iatrogenic hyperthyroxinemia. The starting dose of levothyroxine for those requiring a dose reduction was 13.2 ± 2.4 µg/kg/day. Of the 34% of infants treated with an initial dose of >12.5 µg/day, 57.1% required a dose reduction at follow-up. It is important to note that according to these data and following the guidelines for initiating therapy for CH, 36.5% of infants required a dose reduction for iatrogenic hyperthyroxinemia. It is hypothesized that a narrower range for initial dosing in CH may be appropriate [7].

In a second article, Deng et al. report the incidence of CH in China from the national newborn screening program for the years 2013–2015. So far, only limited data have been available on the epidemiological characteristics of CH in China. In this report, the incidence of neonatal hypothyroidism in China is estimated and its geographical variation in this large country is described. Poisson regression was used to generate the odds ratios (ORs) and 95% confidence intervals (CIs) between the rates of thyroid dysfunction and selected demographic characteristics and geographical locations. A total of 18,666 cases with CH were identified from 45.2 million newborns, yielding an overall incidence rate of 4.13 per 10,000 live births. Compared with those in remote areas, regardless of infant sex, a higher incidence risk for CH was present in newborns in the coastal areas and inland areas (females: OR = 2.00, 95% CI: 1.86–2.16 and OR = 1.74, 95% CI: 1.61–1.87, respectively; males: OR = 1.70, 95% CI: 1.59–1.83 and OR = 1.52, 95% CI: 1.42–1.63, respectively). Additionally, the highest risk of neonatal hypothyroidism for TSH screening values less than 40 mU/L was observed among neonates in the coastal areas, while TSH screening values of 70–100 mU/L were observed among those in the inland areas. The authors conclude that the overall incidence of CH is high in China. In addition, there is a significant geographical variation in the incidence of hypothyroidism [8].

In another paper from Asia, the incidences and underlying causes of CH before and after the implementation of a neonatal TSH screening program in southern Thailand are reported by Jaruratanasirikul et al. In Thailand, neonatal

TSH screening was only implemented nationwide in 2005. In this study, the medical records of pediatric patients who were diagnosed with primary hypothyroidism at one center during the period between 1995 and 2013 were retrospectively analyzed. The most common form of CH during the study period 1 (SP1) was overt permanent CH (66%), mostly caused by athyreosis or ectopic thyroid. The overall annual incidence of congenital hypothyroidism per 10,000 live births in southern Thailand, namely Songkhla Province, was 1.69 (1:5021) and 4.77 (1:2238); and in all 14 provinces in southern Thailand the estimated incidence was 1.24 (1:8094) and 2.33 (1:4274) in a later time period [9].

Lastly, the current status of the CH neonatal screening program in Adana Province, Turkey, is analyzed by Kör and Kör [9]. The analysis results of 1300 infants who were referred to the regional endocrinology polyclinic because of suspected neonatal hypothyroidism were retrospectively evaluated. The mean capillary and venous TSH levels of 223 patients identified with hypothyroidism were 40.78 (5.5–100) $\mu\text{IU/mL}$ and 67.26 (10.7–100) $\mu\text{IU/mL}$, respectively. The screening time was 8.65 (0–30, median: 7) days postnatally. The duration between heel prick time and venous TSH time was 11.10 (2–28, median: 11) days and longer than planned (3–5 days). The authors conclude that although the duration for the diagnosis and initiation of treatment of CH were markedly reduced with the implementation of the screening program in Turkey compared to those before the implementation of the screening program, the targeted and ideal time was not reached for the initiation of final diagnosis and treatment (≤ 14 days) [10].

In conclusion, the articles presented in this issue report on the incidence of CH in China, Turkey and Thailand. No conclusive data on congenital hypothyroidism had been available from these regions before, and quality management and analysis of timelines for the initiation of treatment need to be expanded for all screening programs worldwide. Without quality control and analysis of efficacy and clinical value, neonatal screening programs cannot achieve their goal which is to prevent cognitive impairment and severe mental retardation in children affected by congenital thyroid disease [10].

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