Best Practice & Research Clinical Endocrinology & Metabolism 28 (2014) 133–150

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

1

Genetics of normal and abnormal thyroid development in humans

Gabor Szinnai, MD, PhD, Senior Lecturer [a, b, *]

[a] Division of Paediatric Endocrinology and Diabetology, University Children's Hospital Basel UKBB, Spitalstrasse 33, CH-4031 Basel, Switzerland
[b] Department of Biomedicine, University Basel, Spitalstrasse 33, CH-4031 Basel, Switzerland

Keywords:
thyroid development
thyroid dysgenesis
congenital hypothyroidism
thyroxine
neonatal screening
endoderm
epigenetics
Mendelian inheritance

The most frequent cause of congenital hypothyroidism is thyroid dysgenesis. Thyroid dysgenesis summarizes a spectrum of developmental abnormalities of the embryonic thyroid ranging from complete absence of the thyroid gland (athyreosis), to a normally located but too small thyroid (hypoplasia), or an abnormally located thyroid gland (ectopy). Although considered a sporadic disease, distinct genetic forms of isolated or syndromic thyroid dysgenesis have been described in recent years. However, genetics of thyroid dysgenesis (TD) are mostly not following simple Mendelian patterns, and beside monogenic, multigenic and epigenetic mechanisms need to be considered.

The review will highlight the molecular mechanisms of thyroid organogenesis, clinical and genetic features of the different monogenetic forms of thyroid dysgenesis, the aspects relevant for diagnosis and counseling of affected families and current research strategies to get more insight into the non-Medelian mechanisms of normal and abnormal thyroid development.

Congenital hypothyroidism

Definition and classification

Congenital hypothyroidism (CH) describes a hormonal state of insufficient thyroid hormone secretion detected at birth or postnatally, present already *in utero*. In iodide-sufficient areas congenital

* Division of Paediatric Endocrinology and Diabetology, University Children's Hospital Basel UKBB, Spitalstrasse 33, CH-4031 Basel, Switzerland. Tel.: +41 61 704 2922; Fax: +41 61 704 1213.
E-mail address: gabor.szinnai@unibas.ch.

1521-690X/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.beem.2013.08.005

thyroid insufficiency results from abnormalities at any level of the hypothalamic–pituitary–thyroid axis [1–3].

Primary CH is due to defects within the thyroid gland parenchyma, while secondary or tertiary CH, also summarized as central CH, is caused by defects in the pituitary gland or the hypothalamus. Primary CH is characterized by high thyrotropin (TSH) levels reflecting the degree of thyroid hormone deficiency by the missing negative feedback on the pituitary and the hypothalamus. Central CH is associated with low to inadequately low normal TSH values in the context of low thyroid hormone levels [1–3].

CH can be divided into a permanent form, which needs life-long substitutive treatment and a transient form that resolves weeks to months after birth. The most common etiology of primary permanent CH is thyroid dysgenesis (TD: OMIM 218700). It occurs in 80–85% of patients with primary CH and is a consequence of abnormal thyroid gland organogenesis. In 10–15% of cases, primary CH is caused by inherited defects of thyroid hormone biosynthesis, also called thyroid dyshormonogenesis (TDHG; OMIM 274400–274900) [1–5].

Clinical aspects and neonatal screening

Although exposed to CH already *in utero*, most infants born with CH are asymptomatic. Less than 10% showed clinical signs and symptoms at birth in the pre-screening era, according to Alm et al. [6,7]. Symptoms develop slowly over weeks and are initially non-specific. The most prevalent symptoms are prolonged jaundice, feeding difficulty, and lethargy. Further features can be macroglossia, large posterior fontanel, while goiter is only associated with dyshormonogenesis but not with TD [1–5].

Normal thyroid hormone levels are of utmost importance for normal cerebral development and subsequent neurocognitive development during gestation and infancy [8]. In iodine-sufficient areas fetal thyroid hormone deficiency can partially be compensated by trans-placental transfer of maternal thyroid hormones [9]. However, after birth, infants suffering from CH are completely dependent on their own thyroid function. Depending on the biochemical severity of thyroid deficiency these infants develop overt hypothyroidism in the first weeks or months postnatally. During the first two years postnatally, brain development is still strongly dependent on thyroid hormones, and deficiencies during this critical time window will cause irreversible neurocognitive and intellectual deficits [8–10].

Thus, the clinical importance of CH stems from the fact that CH is the most frequent preventable cause of mental retardation. Introduction of neonatal screening programs in the 1970ies allowed to detect and treat affected neonates before clinical signs appeared, preventing the devastating effects of prolonged postnatal hypothyroidism on neurocognitive development [3,11]. Neonatal screening is until today the most cost-effective secondary prevention measure of modern medicine [3,12,13] by ensuring practically normal intellectual function even in patients with most severe forms.

Incidence

CH is the most common congenital endocrine disorder. Primary CH occurs in about 1:1600–3400 newborns, depending on neonatal screening TSH thresholds, while secondary or tertiary CH is rare (1:50,000 newborns) [14–18]. Different incidence rate of CH in different populations have been reported by several authors [15,16]. The most recent demographic study form New York State by Harris et al. confirmed earlier data, showing highest incidence in the Asian population (1:1016) followed by the Hispanic (1:1559), the White (1:1815) and the American Black (1:1902) population [19].

Increased global incidence of primary CH was reported by some authors over the past decade. In the United States, this observation was associated with a higher frequency of milder forms and demographic factors, especially increasing number of births among the Hispanic population [20,21]. In European countries and Canada, higher incidence was rather associated with lowering of TSH screening thresholds [18,22,23]. The most detailed single center study with scintigraphic characterization of the complete study cohort over 20 years clearly showed, that the apparent increased incidence was in fact solely the result of the lowered TSH cutoff and that the additionally identified patients suffered from predominantly mild forms of CH [18].

It is noteworthy, that despite lowering of TSH thresholds and identification of more mild forms of CH, most of these cases (75–86%) were permanent and not transient [18,22,23].