AETIOLOGY AND TREATMENT OF CONGENITAL HYPOTHYROIDISM

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In the past a minority of children with congenital hypothyroidism (CH) were clinically detected. The diagnosis, nowadays, is based on neonatal screening and the confirmation of the disorder obtained by measuring plasma TSH and T4.Measurement of plasma thyroglobulin, thyroid US and scintigraphy are useful for a better classification of the disease. Plasma T4 and T3 as well as bone X ray of the knee are good indicators of the severity of fetal hypothyroidism.

The incidence of CH is quite stable across countries and is about 1:3 000 to 4 000 newborns with the exception of African American population where the incidence is around 1:10 000 newborns.

It is well known that this disorder is sporadic but there are also familial forms in about 2% of the cases.This observation is strongly in favour of a genetic contribution to developmental anomalies of the thyroid gland.

Studies in knockout mice have demonstrated a critical role for several genes in the early events of thyroid organogenesis. To date, 4 genes have been involved; three of them encode transcription factors while the other encodes the thyrotropin hormone receptor (TSHR). In mice, Ttf-1 inactivation leads to absence of thyroid tissue associated with severe defects in the lung and the forebrain, indicating a critical role of this factor in early events of organogenesis. Ttf-2 inactivation has revealed that this factor is required for the downward migration of the thyroid gland as well as for palate closure, with knockout mice showing either athyreosis or ectopic gland associated with cleft palate. Pax 8-knockout mice demonstrated severe thyroid hypoplasia with complete absence of follicular structures whilst defects in TSH secretion and action (like in TSHR inactivation) are associated with a small orthotopic thyroid gland, indicating that the action of TSH through its receptor is not required for migration but is essential for the proliferation and for the maintenance of the differentiated function of the thyroid follicular cells.

That these genetic factors may be involved in the pathogenesis of TD in humans is supported by recent reports which have identified germline mutations of these 4 candidate genes in about 20 patients with TD.

Homozygous *TTF-2 (*or *FOXE1)* mutations are reported in 2 familial cases of athyreosis associated with cleft palate and choanal atresia in one case. This association, known as Bamforth syndrome, is consistent with the developing expression profile of TTF2.

Heterozygous *TTF-1 (*or *NKX2.1)* mutations produce a predominantly neurological phenotype (choreo-athetosis) with possible pulmonary lesions, that is associated with generally mild thyroid dysfunction with a normal or hypoplastic thyroid gland.

Heterozygous mutations of *PAX8* have been identified in some families with an isolated thyroid phenotype (consisting of an orthotopic thyroid hypoplasia) that may be associated with cystic lesions and kidney malformations e.g. unilateral renal agenesis and a left sided uretero-pelvic obstructio. All of these associations are in keeping with experimental evidence that the proteins are expressed in several other developing organs, respectively lung and ventral forebrain for Ttf1, and kidney for Pax8.

Inactivating mutations of the *TSHR* gene, either homozygous or compound heterozygous have been observed in a few cases of thyroid hypoplasia.

Therefore, taken together, these data argue in favour of a significant genetic contribution in TD, implicating at least these 4 candidate genes.However, despite intensive research programs throughout the world, abnormalities in these 4 genes have been found in only a small proportion of TD cases, most of them with syndromic phenotypes, suggesting that none of them is a major genetic factor in this disorder and that other genes may be involved. A linkage analysis performed in 19 TD multiplex families supported this view showing the exclusion of the 4 candidate genes in 5 families that demonstrated for the first time the relevance of other genes

In about 10-20%, the TG has a normal shape(although sometimes enlarged) and location and in this situation there is most probably a defect in one of the genes coding an enzyme or protein involved in the biochemical mechanism responsible for thyroid hormone synthesis. These are: sodium iodide symporter gene, thyroglobulin gene, pendrin, thyroid peroxydase (TPO), and thyroid oxydase 1 and 2 (THOX1 and THOX2).These patients present a normal or enlarged gland and the majority has a positive perchlorate discharge test.

The treatment of CH is not modulated by the etiology. The goal is to correct as **soon** and as **quickly** as possible

the state of hypothyroidism by thyroid hormone administration. L T4 is given on a weight basis and a dose of 10 ùg /Kg /Day is usually optimal although a larger dosage might be necessary mostly in the most severe form of hypothyroidism. It is important to educate the parents for compliance so they are full aware of the extreme importance of the LT4 administration. When there is evidence of fetal hypothyroidism (low plasma T3, absence of distal femoral epiphysis calcification) a more specific surveillance and evaluation of psycho-motor development is necessary .Appropriate care might be necessary if there is evidence of delayed development.

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