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Congenital Hypothyroidism

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<http://dx.doi.org/10.5772/54660>

1. Introduction

Congenital hypothyroidism is the most frequent congenital endocrine disorder and preventable cause of mental retardation. The remarkable irreversible mental damage can be avoided by the replacement therapy introduced before the age of 3 weeks. Therefore a screening program implemented in the early seventies to pick up the affected babies on the first weeks of life [1,2]. After pilot studies started in 1977 a national neonatal TSH screening program was introduced in Hungary in 1982 [3]. It has continued in two centers from 1984 covering the whole country (50-50 % of the expected newborns were assigned to one lab). Patients screened and confirmed as CH were followed-up at the endocrine outpatient clinics. Replacement was adjusted according to the laboratory results and somatic-mental development of the child. The authors (two pediatric endocrinologists and one psychologist) have worked together in this project throughout 26 years in one of these centers. They present their experiences with the screening program and the endocrine/psychological follow-up gained during this period discussing the results with literature data.

The widely known incidence data on congenital hypothyroidism before the introduction of neonatal screening originate from the North European countries: 1 to 6000-10000 [4-6]. Nowadays when the usage of the national language is increasingly accepted in authentic translation at the international forums the Hungarian contribution may be interesting. The Thyroid Work Group of Hungarian Pediatric Institute collected five years incidence data (1966-70) from the pediatricians all over the country and "... 40/year new hypothyroid children were reported". The birthrate was 160.000/year that time, so the incidence was calculated 1:4000, published in Hungarian in 1972 [7]. This numerical value almost corresponds to the data experienced by the neonatal screening.

According to the recent data the incidence of congenital hypothyroidism varies from 1:1000 to 1:3500 life births depending on the iodine sufficiency, demographic and other unknown factors

as well as on laboratory methods and screening practice. Several work groups noted a progressively rise since the early 1990s both in America and Europe [8-16], however the question was raised with reason: “Was this increasing incidence real ... or was ... an artifact, explained by modifications of screening programs such as a change in test cutoffs?” (LaFranchi 2011; [13]. According to a convincing Canadian study the incidence of thyroid dysgenesis, which form is more than 80 % within the CH, has remained relatively stable over the last decades [9,15]. Demographic factors were “suspected” to be responsible for this phenomenon [8] but it was not confirmed as a complete explanation [9]. The changes in test cutoffs [13,14] or simply the used different laboratory and screening methods in certain centres [17] might be also the first candidates behind the increasing incidence rate in some screening programs. These data “highlight the need for consensus development regarding the diagnosis and treatment of congenital hypothyroidism” according to Rapaport’s commentary [18] to one of these reports [12]. And indeed, recently (November 2011) recommendations were prepared at the ESPE consensus meeting (complete version is in press) for orientation relating to the screening, investigation, treatment, long terms outcomes and genetic/antenatal diagnosis in CH [19].

In Hungary the screening program is based on primary TSH determination and the overall incidence of CH is 1:3316, namely 413 cases were diagnosed out of 1,369.503 newborns screened between 1982 and 2007 in our Screening Center. The annual incidence is relatively constant (Figure 1.). Opposite to primary T_4/FT_4 measurement with backup TSH determination it was not necessary to change the cutoff levels of TSH for increasing the sensitivity and other conflicting factors could be avoided, namely the low FT_4 levels of preterm babies and obtaining the blood specimens remarkably earlier.

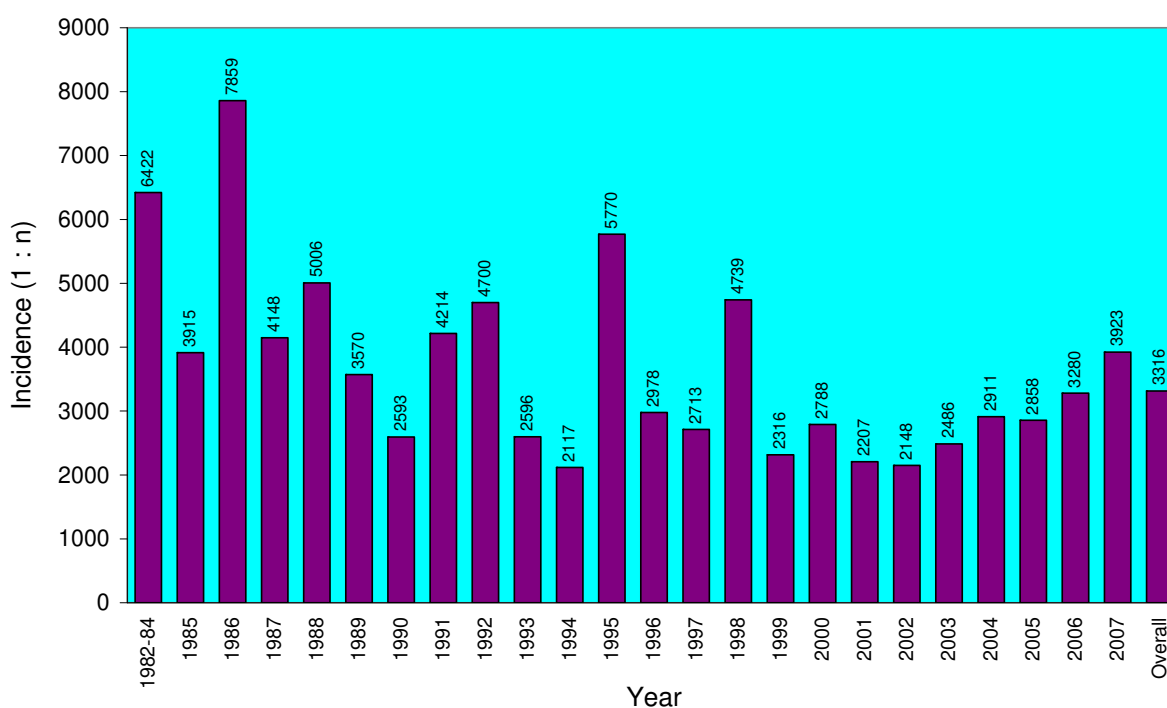


Figure 1. Annual incidence of congenital hypothyroidism

Most of the cases detected in newborn age have permanent hypothyroidism caused by abnormal thyroid gland development (dysgenesis) or that of inborn error of thyroid hormoneogenesis (dyshormonogenesis). Thyroxine-binding globulin (TBG) deficiency occurs in 1 to 9000 live births, while congenital central hypothyroidism (TSH and/or TRH deficiency) occurs in less than 1:20000-100000. Transient hypothyroidism may occur because of delay in maturation of the hypothalamic-pituitary-thyroid axis, both iodine deficiency and excess, dysfunction of the mother-placenta-fetal unit or the effect of medication used on the intensive care unit. Both monoallelic and biallelic mutations in DUOX2 gene result transient CH reported recently [20,21]. Permanent CH patients need a life-long treatment while transient cases can quit of replacement after recovery of thyroid function.

As the postnatal development of the nervous system is thyroid hormone dependent up to 2-3 years none of the patient were put on higher risk by suspend the therapy to early therefore the revision of the neonatal diagnosis was postponed above the age of 2-3 years. Classifying the disorder as permanent or transient was obtained on abnormal or normal hormone levels after withdrawal of levothyroxine replacement. Before 2 years of age the following course of the disease was suspicious for transient dysfunction of the thyroid. Shortly after the introduction of replacement therapy TSH normalized and never increased above the upper limit parallel with decreasing demand of levothyroxine to keep T4/FT4 in the reference range. In 21 patients out of 291 substituted infants we could simply withdraw the replacement and the TSH remained normal.

Above the age of 3 years a T3 withdrawal test was performed in 197 children to reconsider the diagnosis of CH. We applied the same method for all patients: L-T4 was shifted to L-T3 for 3 weeks, which has a shorter half-life. After one week L-T3 was also stopped, patients were off-treatment altogether for one week. At the end of the 4th week presenting a normal thyroid function test is considered to be a transient hypothyroid case. Five out of 197 patients tested have proven transient CH. The total number of children reached 3 years of age and who were old enough for T3 withdrawal test were 310, which give the overall transient CH rate as 8.4 % (21+5/310).

2. Methodology

From the very beginning up to the end of 2007 we used a primary TSH screen and a secondary serum thyroid hormone measurement to confirm the abnormal TSH results. A drop of whole blood was obtained and dried on filter paper between the ages of 3-5 days. Samples were sent to the assigned screening laboratory via mail. Measurement of TSH was performed after an elution process using a home-developed RIA until 1993 [21,22]. Cessation of the cheap antibody supply forced us to buy commercial kits changing for DELFIA, LIA, IRMA and ELISA methods. All tests offered narrower measuring ranges and cutoff values became more precise. The algorithm for selection of specimen for further evaluation was very simple. Samples below the cutoff level (25 μ U/ml later on 20 μ U/ml) were considered as normal, between the range 25(later on 20)-50 as suspected positive and above 50 μ U/ml as true positive. Technical errors

were ruled out by repeated measurement from the blood spot and only samples above the cutoff limit were recognized and infants were called to visit us immediately. Physical examination and blood sample were taken for peripheral thyroid hormones and TSH measurement from the serum. The diagnosis of CH was confirmed by low T4/FT4, T3/FT3 levels and elevated TSH.

2.1. Etiology

Almost 95% of cases born with CH have primary hypothyroidism reflecting peripheral defects and less than 5% has secondary/tertiary hypothyroidism results from lack of TSH and/or TRH production. Both the presentation and the sequel of the congenital central hypothyroidism are less severe although most commonly it is part of a disorder causing congenital hypopituitarism. Several imaging methods are suitable to describe the position and size of the thyroid. Localization or absence of the gland helps to differentiate dysgenesis and dysmorphogenesis in CH patients.

I¹²³ scan is optimal to test the newborn babies for possible developmental defect of the thyroid gland before replacing them but it was not available for us. During replacement therapy the background of thyroid dysfunction was tested using different imaging techniques. Ultrasonography is a non-invasive method but requires a baby-head for apparent description of a tiny or absent gland. Thyroid scintigraphy is a more precise but invasive method requiring an unreplaced situation. Scintigraphy was performed in 182 cases combined with T3-withdrawal test. Thyroid dysgenesis occurred in 84% (agenetic: 47%, ectopic lingual: 28%, hypoplastic: 9%), an enlarged thyroid was seen in 6% and a normal-sized eutopic gland – so-called “thyroid in situ” [12,13] – in 10%.

Further distinction of etiology is offered by molecular genetics. Several genes involved in thyroid ontogenesis and in normal function of it. An abnormal expression of the thyroid specific genes can be manifested in different phenotype, which is summarized in Table 1.

Gene	Chromosome region	Role of gene in organogenesis/ protein function	Phenotype (by morphology or function)	Associated disorders
DYSGENESIS				
TITF1/NKX2.1	14q13	<i>Development of both follicular and C-cells</i>		Choreoathetosis, RDS, pulmonary disease
PAX8	2q12-q14	<i>Thyroid follicular cell development</i>	Aplasia or Hemiagenesis or Hypoplasia (with or without ectopy)	Renal agenesis
TITF2/FOXE1	9q22	<i>Migration of thyroid precursor cells</i>		Cleft palate, choanal atresia, bifid epiglottis, spiky hair (Bamforth-Lazarus sy.)
GNAS1	20q13.2	Signalling protein	<i>Resistance to thyrotropin</i>	Osteodystrophy (hereditary Albright sy.)

Gene	Chromosome region	Role of gene in organogenesis/ protein function	Phenotype (by morphology or function)	Associated disorders
TSHR	14q31	<i>Thyroid differentiation</i> Thyrotropin receptor	Hypoplasia (without ectopy) <i>Resistance to thyrotropin</i>	-
INBORN ERROR OF THYROID HORMONOGENESIS				
TITF1, PAX8, TITF2/ FOXE1	See above	During later stages: <i>Regulation of thyroid specific gene expression</i>		-
TPO	2p25	<i>Thyroid differentiation</i> Iodide organification		-
TG	8q24.2-q24.3	<i>Thyroid differentiation</i> Structural prohormone		-
NIS	19p13.2-p12	Iodide transport from the blood into thyroid cell (basal membrane)	Enlarged thyroid gland	-
PDS	7q31	Iodide transport from thyroid cell to follicular lumen (apical membrane)		Sensorineural deafness (Pendred sy.)
DUOX1/THOX1 DUOX2/THOX2	15q15.3	Thyroidal H ₂ O ₂ generation		-
DUOXA2	15q21.1			
IYD/DEHAL1	6q24-q25	Deiodination for iodide recycling		-
THYROID HORMONE TRANSPORTER DEFECT				
MCT8	Xq13.2	Transmembrane T ₄ , T ₃ , rT ₃ , T ₂ transport	<i>Thyroid hormone resistance</i>	Severe neurological abnormalities (Allan- Herndon-Dudley sy.)
THRB	3p24.3	Nuclear thyroid hormone receptor		Hyperactivity, learning disability
SBP2	9q22.2	Synthesis of selenoproteins	<i>Abnormal TFT</i>	Delayed puberty (?)
IMPAIRED HYPOTHALAMIC-PITUITARY-THYROID AXIS				
LHX3	9q34.3	<i>Early pituitary development</i>		CPHD, pituitary mass, rigid cervical spine
LHX4	1q25		<i>Secondary/tertiary hypothyroidism</i>	CPHD, sella turcica defect
PROP1	5q	<i>Expression of all pituitary cell lineage</i>		CPHD, pituitary mass

Gene	Chromosome region	Role of gene in organogenesis/ protein function	Phenotype (by morphology or function)	Associated disorders
POU1F1	3p11	Generation and cell-type specification		GH, PRL deficiency
HESX1, PHF6	3p21.2-p21.1	Forebrain, midline and pituitary development		Septo-optic dysplasia, CPHD, epilepsy
TRHR	8q23	TRH receptor		-
TSHB	1p13	TSH β subunit		-
OTHER				
DUOX2/THOX2 DUOX/DUOXA	15q15.3	Partial defect in H ₂ O ₂ production	Transient CH	-

CH= Congenital hypothyroidism, CPHD = Combined pituitary hormone deficiency, GH = Growth hormone, PRL = Prolactine, RDS = Respiratory distress sy, TFT = Thyroid function test

Table 1. Thyroid specific genes involved in congenital hypothyroidism [23-39]

A cohort of 58 patients was analyzed for PAX8 (exon2 and exon3) mutation. Genetic screening did not reveal any mutation on the PAX8 gene in children with thyroid dysgenesis. It supports the recent notion that non-syndromic thyroid dysgenesis is rather a heterogeneous disease than a monogenetic one. Up to now the exact etiology of CH remained unknown for the great majority of the cases. More candidate genes have been verified in syndromic CH patients as distinct gene loci can be connected to distinct clinical feature. Analyzing our cohort congenital malformations were found in 45 cases (Table 2.) and concomitant disorders in 46 cases out of 210 CH patients (Table 3) [40]. Phenotypes specific gene on selected CH patients with associated disorders should be analyzed to gain more information on fetal thyroid development. Recently Park and Chatterjee proposed an algorithm for investigating the genetic basis of congenital hypothyroidism [41].

Malformations, syndromes	Male	Female	Cytogenetic location
Congenital heart disease	6	3	
Renal malformation		5	
Urogenital malformation	11	2	
Musculoskeletal malformation		3	
Scoliosis	2	1	
CNS malformation	1	1	
Dysmorphic auricle/face	2	2	
Pulmonary fibrosis		1	

Malformations, syndromes	Male	Female	Cytogenetic location
DiGeorge sy.	1		22q11
Kabuki make-up sy.		1	8p22-23.1
Marfan sy.		1	15q21.1
Mayer-Rokitansky-Küster-Hauser sy.		2	1p35
CNS = central nervous system			

Table 2. Congenital malformations found in CH patients (45/210)

Impaired function	Male	Female
Delayed speech development	3	4
Stammer	2	
Behavioral problem	3	4
Delayed motor development	1	1
Disturbed motor coordination	2	2
Nocturnal enuresis		7
Strabismus	3	1
Congenital nystagmus		1
GORD	1	2
Epilepsy	1	
Malignancy		2
Serious infection	2	
T1DM	1	
Angioedema		1
GORD = gastro-oesophageal reflux disease, T1DM = type 1 diabetes mellitus		

Table 3. Concomitant disorders found in CH patients (46/210)

2.2. Clinical signs

The classical picture of CH with characteristic clinical features develops by the age of three months with irreversible neurological damage. Non-specific signs and symptoms can be noticed during the first weeks of life, which help to set the diagnosis of CH in screened but not confirmed newborns. During the first 10 years of screening program all newborns identified by an abnormal TSH were admitted to the hospital and were assessed by history and complete physical examination. More than 10 unspecific symptoms and history data recorded of 87 suspected babies were analysed to identify any factors that could predict congenital hypo-

thyroidism. Based on confirmatory laboratory results 67 babies out of 87 proved to have CH (true positive or CH group) and 20 was false positive (reference group). Between the two groups 8 parameters (opened posterior fontanel, umbilical hernia, dry skin, enlarged tongue, constipation, laziness, wide nasal bridge, and prolonged jaundice) were found to have significant differences by linear discriminant analysis that were ranked and weighted for scoring. An additional score was calculated from the blood-spot TSH namely the quotient of measured TSH and the cutoff limit for normal thyrotropin. Figures above 6 were correct for predicting CH in 99% of cases. This score system developed (Table 4.) advises the clinicians to pick up and replace the affected babies earlier than 3 weeks of age [22,42].

Clinical sign	Score	Clinical sign	Score
Opened posterior fontanel	2	Constipation	1
Umbilical hernia	2	Laziness	1
Dry skin	2	Wide nasal bridge	1
Enlarged tongue	1	Prolonged jaundice	1
Blood spot TSH: Quotient of measured and cutoff limit for normal			1
Cutoff value for predicting CH			" /> 6

Table 4. Score system for predicting congenital hypothyroidism using primary TSH measurement

2.3. Endocrine and psychological care

2.3.1. Thyroid hormone replacement

The timing of T_4 -level's normalization is crucial to the neuropsychological development therefore the first aim of the neonatal screening programs is to reach the earliest start of the hormone replacement. At the beginning the intervals between the birth and start of T_4 replacement were reduced in length as follows: in 1985: 25 ± 5 days, in 1987: 20 ± 9 and in 1990 18 ± 9 days. This length of time improved to ≤ 14 days on average after the introduction of one-day TSH assays and successful education of the personnel involved.

Concerning the dosage and the formulation of thyroid hormone replacement let us call to mind some of our former results, namely in the 1980s both lower and higher thyroxin doses were applied [43–49]. In our early study [22,50] the higher $L-T_4$ dose was found to be more effective than the lower one (Table 5). It was confirmed recently also by the Glasgow-group recommending the $50 \mu\text{g}$ initial dose on the basis of their results in 314 children with CH [51]. In our program $10\text{--}15 \mu\text{g}/\text{kg}$ as an initial dose is used since the middle eighties [22,42].

At the beginning of our TSH-screening pilot studies (in the early seventies) the synthetic $L-T_4$ preparations were not available in Hungary, therefore the thyroid hormone replacement was started with oral administration of thyroid extract (thyreoidea sicca: Thyranon, Organon). Later on we changed to the $L-T_4$ monotherapy and according to our first impressions the

Number of children		22	13		
Dose of L-T ₄		25 µg	6,6 µg/kg	50 µg	13,4 µg/kg
Starting values	T ₄ (µg/dl)	3,3 ± 2,9		3,6 ± 3,5	
	T ₃ (ng/ml)	1,14 ± 0,77		1,34 ± 0,59	
	TSH (mIU/L)	75,1 ± 16,3		74,9 ± 10,4	
Values at first visit	T ₄ (µg/dl)	13,2 ± 3,9		18,9 ± 3,6	
	T ₃ (ng/ml)	2,2 ± 0,65		2,09 ± 0,33	
	TSH (mIU/L)	29,1 ± 31,4		1,0 ± 0,9	
Interval (days)		28 ± 35		19 ± 7	

Normal values: T₄: 9,0-15,0 (newborn: -20,0) µg/dl; T₃: 1,5-3,5 (newborn: -4,0) ng/ml; TSH: 0,5-5,0 (newborn: -20,0) mIU/L

Table 5. Correlation between starting L-T₄ dose and changes of thyroid parameters during hormone replacement

Thyranon proved to be more effective at least regarding the decrease of TSH level [22,50]. It was confirmed in our systematic study but the increase of T₃ level was also detectable (Table 6.)

	T ₄ (µg/dl)		T ₃ (ng/ml)		TSH (mIU/L)	
	at start	at control	at start	at control	at start	at control
Thyranon (T ₃ +T ₄) n = 21	3,0 ± 2,6	11,3 ± 4,2	1,15 ± 0,51	3,07 ± 1,70	73,84 ± 10,49	13,16 ± 26,35
L-Thyroxin (T ₄) n = 22	3,3 ± 2,9	13,0 ± 3,9	1,3 ± 0,77	2,2 ± 0,65	75,19 ± 16,30	29,10 ± 31,41
Thyranon⇒L-T ₄ n = 19	before	after	before	after	before	after
	10,4 ± 3,2	11,9 ± 2,4	2,63 ± 0,96	2,03 ± 0,66	13,75 ± 22,21	14,13 ± 16,79

Normal values: T₄: 9,0-15,0 (newborn: -20,0) µg/dl; T₃: 1,5-3,5 (newborn: -4,0) ng/ml; TSH: 0,5-5,0 (newborn: -20,0) mIU/L

Table 6. Changes of thyroid parameters on T₄ or T₄ + T₃ replacement

At that time our conclusion was: “these results confirm the suggestion that T₃ may play a more important role than T₄ in regulating the serum TSH concentration” [50].

One of the main goals of thyroid hormone replacement in congenital hypothyroidism is to reconstitute the biochemical euthyroidism (the TSH and thyroid hormone levels into the reference ranges) to avoid the prolonged hyperthyroxinemia and the permanent overproduction (or suppression) of thyrotropin. The most important period to monitor the adequate thyroid hormone replacement is the first three years of life to ensure optimal somatic and psycho-neurological development. Our practice harmonize the recent recommendation: follow-up

every 1-2 months in the first 6 months, every 2-3 months between 6 months and 3 yrs of age and every 6-12 months later in childhood [52,53].

There are warning data on the importance of well-organized care of children with CH. According to a new American publication based on health insurance claims data of 704 children with presumed CH 38 % (!) discontinued replacement of thyroid hormone within the first 3 yrs of life [54]. In another smaller cohort (140 children) 48,6 % were lost to follow-up (!); of the 72 patients who were re-evaluated at age 3 yrs, treatment had been stopped without medical supervision in 15 [55]. The puberty and adolescence are the most critical periods regarding the compliance in our experience.

In our practice another unexpected alteration has been occurred during the long and continuous follow-up. In a few cases with stable FT₄/TSH relation for many years under gradually increased L-T₄ dose according to the somatic development and TSH-FT₄ values, later we measured elevated TSH despite high FT₄ levels almost regularly. On the basis of our good experience with Thyranon (L-T₄ + L-T₃) replacement therapy in the 1970s, we tried to normalize both serum TSH and FT₄ level administered combined L-T₄ and L-T₃ treatment in these patients. Applying an L-T₄/L-T₃ dose ratio between 13:1 and 18:1 by weight, this modification of therapy mostly proved to be successful (one exemplar on Table 7). The dose of L-T₄ was reducible in some other patients. Unfortunately once-daily slow-release formulation of L-T₃ [56] was not available for us.

Age (year)	TSH (mIU/L)	FT ₄ (pmol/L)	FT ₃ (pmol/L)	L-T ₄ µg/day	L-T ₃ µg/day
12	13,24	19,43	5,1	125	-
14,5	11,25	18,7	5,4	150	-
15	6,59	22,26	5,5	150	-
15,5	9,35	20,18	5,8	150	-
16,5	2,25	11,24	5,8	100	20
16,75	3,30	12,80	9,0	125	10
17	6,05	16,14	5,8	150	10
17,25	2,20	19,96	6,9	150	10

Table 7. Some data from the last six years of an adolescent boy

Recently the use of L-T₄ + L-T₃ in the treatment of hypothyroidism is one of the "hot topics" in thyroidology (see excellent papers [57,58] and "2012 ETA guidelines" [59]), however our observation is different from those. These children and adolescents do not have hypothyroid symptoms comparing to the adults (5-10 %) and do have elevated TSH (and FT₄) level. The congenital form of hypothyroidism – as an entity – is not included in the ETA guidelines at all [59]); it is restricted on adults with autoimmune hypothyroidism or caused by definitive therapy (radioiodine, surgery). Now we are analysing the data of our patients in this small cohort.

2.3.2. Evaluation of the somatic development

The aim of thyroid hormone replacement is to ensure optimal somatic and neuropsychological development. The evaluation of somatic and psychological parameters is also necessary to control the quality of compliance, what may be disturbed, – as was mentioned before – especially in the adolescent period. The hormone parameters are relative “quick variable”. The state of thyroid hormone supply at the less and less frequent outpatient visits is well reflected in the somatic development, as “slow variable”.

Somatic development was analyzed using the height and bone age data of 83 prepubertal children. *Height* was measured regularly by Harpenden stadiometer and evaluated by Hungarian reference data [60]. *Bone age* was also determined repeatedly up to the disappearance of bone age retardation using the Greulich-Pyle atlas [61]. *Bone mineral density* (BMD) was measured by single photon absorptiometer (SPA; Gamma Works, Hungary) in 46 children (6-17 yrs). Later peripheral quantitative computer tomography (pQCT; XCT2000, Stratec Electronics, Germany) was introduced to determine radial volumetric total BMD and trabecular Z-score values of 91 children (6-18 yrs). The results were evaluated comparing with Hungarian reference data [62,63].

2.3.3. Growth velocity and bone age

The comparison of age and age for height does not show any difference (age: $6,27 \pm 2,65$ yrs; age for height: $6,26 \pm 2,76$ yrs). Bone age was lower than the chronological age ($5,73 \pm 2,77$ yrs; $p = 0$). The regression's line diverges from the theoretical optimum line in the younger age, but the distribution of the values are almost the same on both sides of the “ideal” line in the older than 10 year of age, or more convincing some values indicate bone age retardation under 10 years (Figure 2).

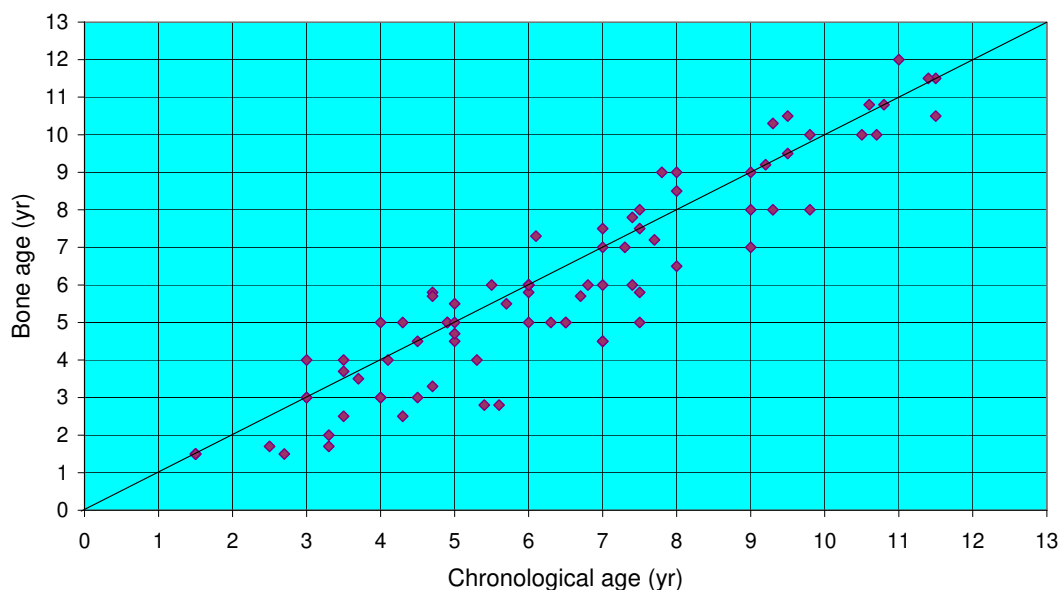


Figure 2. Bone maturation of L-T4 replaced CH patients (n=83)

The publications report usually good results on somatic growth and pubertal development of children with CH detected by neonatal screening and supplemented well with L-T₄ [64-69]. Our results clearly show that the disappearance of bone age retardation is individual. The bone age of children with CH catch up their chronological age in different time at latest about ten years of age.

2.3.4. Bone mineral density

In our first (SPA) study $-0,24 \pm 1,24$ mean Z-score values were found; below $-2,0$ in 3 cases only. After correction to age for height, one value remained under $-2,0$ Z-score [62]. However, SPA may measure false results in growing children (areal BMD; its measure is g/cm²) due to the change of bone size. To avoid this possibility pQCT (volumetric BMD; its measure is g/cm³) measurements were carried out later. The mean total BMD Z-score of 28 boys was $-0,19 \pm 1,18$ and the trabecular BMD Z score: $+0,05 \pm 0,9$, both in the normal range. Similar values were measured in the group of 63 girls: total Z-score $+0,04 \pm 1,15$, trabecular Z-scores $+0,1 \pm 0,98$, but some differences were found in the total density between the younger and older girls (≤ 11 yr $-0,36 \pm 0,9$ and > 11 yr $+0,3 \pm 1,22$). Pathological ($< -2,0$) BMD Z-score did not occur at all among the 28 boys, and only two trabecular density values were in this range among the 63 girls. The total BMD Z-score was found *between* $-1,0$ and $-1,9$ in 5 cases in both groups, the trabecular Z-score value was in this range very rarely (1 and 2 cases respectively).

One of the most important preventive factors of the adult osteoporosis is the attainment of an optimal peak bone mass. Therefore the importance of the good accretion of bone mineral content during the childhood and adolescence is generally recognized. Thyroid hormones are one of the known influencing factors of the BMD. Hyperthyroxinemia can cause bone resorption resulting in a decreased bone mass. BMD was found decreased in adolescent females treated with high doses of L-T₄ [70].

In the first pediatric studies did not measure decreased bone mineral content in children with congenital hypothyroidism by DXA technique [71,72]. Recently slightly decreased BMD values were published within the normal range [73,74], in one publication by quantitative ultrasound technique [73]. In spite of the different methodology what we used (pQCT: direct volumetric method, not mathematically corrected areal one) our conclusion is similar regarding the development of BMD in children and adolescents with congenital hypothyroidism diagnosed at neonatal screening and replaced by L-T₄. Our results are also very slightly lower compared to controls, but the Z-score values are practically always within the reference range.

2.3.5. Final height

In a cohort of 98 children (65 girls) the final height (FH) or nearly FH (growth ≤ 1 cm in the last year) was determined. Results are presented on the table (Table 8.)

The mean value of FH in boys corresponds to the Hungarian reference data and the 3,1 cm difference in the average of girls does not mean significant deviation. In a detailed presentation interesting data were published on "prepubertal and pubertal growth, timing and duration of

	Boys (33)	Girls (65)
Age (yrs)	17,83 ± 2,56	17,47 ± 2,17
Final height (cm)	177,41 ± 5,77	164,11 ± 6,28

Table 8. Final (and nearly final) height of 98 patients with CH

puberty and attained adult height” of 30 patients, included 17 FH values [66]. The authors emphasize the significant positive correlation between the average L-T₄ daily dose administered during the first 6 months of treatment and attained height. We cannot confirm this observation because of our different protocol (uniform L-T₄ dosage was used during the last two decades).

In a Japan publication a greater peak height velocity and pubertal height gain was presented in their male patients [67]; we also observed some difference between the FH of boys and girls to the advantage of the boys.

2.3.6. Menarche

Correct data were gained from 50 girls. Their menarche age is 12,38 ± 1,06 yrs, what is the same as the reference value in Hungary, however the distribution of data is surprising. The manifestation of the first menses happened rather earlier (in 23 girls ≤12 yrs) or later (in 19 girls ≥ 13 yrs) than close to the mean (8 only) indicating the relationship between the thyroid hormone and sexual hormone axes. Italian authors differentiated two groups of girls according to their menarche age (11,5 ± 0,8 yrs versus 12,6 ± 1,2 yrs) like us but both groups attained normal FH similarly to our results [68].

3. Evaluation of psychoneurodevelopment

The somatic development is almost perfect in the children with CH detected by neonatal screening and had optimal thyroid hormone replacement. The same does not apply to their psychoneurodevelopment.

After the first ten years of our neonatal TSH screening program (117 CH/508.590 newborn) the IQ was tested in a cohort of 46 children (39 permanent and 7 transient CH; age 3-8 yrs). Although a normal distribution of IQ values was detected, a strong correlation was observed in 28 children between the IQ and serum thyroglobulin (Tg) level (Tg < 0,3 ng/ml in 3 out of 21 with IQ > 90 and 4 out of 7 with IQ < 90; p < 0,01 using Yates correction). This early data confirmed the thesis [75,76] that although there is some placental transfer of thyroid hormones during pregnancy, it cannot totally prevent the intrauterine neurological damage in athyroidism [77].

Ten years later we presented more detailed results on the neurodevelopment of CH children [78,79]. The main message is summarized on the next table (Table 9.) The correlation between the date of diagnosis, serum T₄ level before start of replacement, initial L-T₄ dose and the IQ of 58 children (born 1985-95; tested 1993-2000 at age 4,9 ± 2,0 yrs; repeatedly tested 49 of them

at age $8,5 \pm 2,5$ yrs) were analyzed. According to these data the onset of replacement before 2 weeks of life in the newborns with serum T₄ level $< 3 \mu\text{g/dl}$ ensure the best IQ; similar data are published [46,47,49].

Serum T ₄ $< 3 \mu\text{g/dl}$				
Start of L-T ₄ replacement (day)				
	7-13		14-26	
Dose of L-T ₄ $\mu\text{g/kg/day}$	< 10	≥ 10	< 10	≥ 10
Number of patients	3	3	15	8
IQ values	$106,3 \pm 8,0$	$108,7 \pm 26,5$	$101,4 \pm 12,2^*$	$101,4 \pm 11,4$
Serum T ₄ $\geq 3 \mu\text{g/dl}$				
Start of L-T ₄ replacement (day)				
	7-13		14-26	
Dose of L-T ₄ $\mu\text{g/kg/day}$	< 10	≥ 10	< 10	≥ 10
Number of patients	6	5	14	4
IQ values	$115,0 \pm 6,7$	$113,6 \pm 13,6$	$103,6 \pm 8,4$	$103,8 \pm 12,8$

* p = 0,05

Table 9. Relationship between some important parameters and the IQ in replaced children with CH

With these experiences we realized the need of regular psychological care. One of us (R.G.) performs this work continuously connecting the endocrine outpatient clinic. Every patient is tested at least once a year.

The recently prepared DQ and IQ results are presented on the next table (Table 10).

Age (year)	Number of patients	DQ/IQ values	Test-methods (norm.: 90-110)
< 3	175	$99,65 \pm 13,0$	Brunet-Lésine
3-8	146	$104,44 \pm 12,7$	Binet
8-10	136	$106,3 \pm 10,59$	Binet
14-16	30	$93,25 \pm 7,22$	WISC-IV*

*Wechsler Intelligence Scale for Children 4th ed. (total quotients). The Processing Speed Q: $95,07 \pm 12,74$; Verbal Q: $92,81 \pm 11,69$; Performance Q: $92,55 \pm 14,63$ and Working memory Q: $89,92 \pm 14,95$.

Table 10. Developmental and intelligence quotients

The DQ and IQ test-results of the first three age groups are in the normal range. Some neurocognitive abilities might be affected in these children (visuospatial-, visuomotor-, language and speech-, attention and memory).

If the DQ value tested by Brunet-Lésin method suggests a delay in development, we can intervene early enough to help the children. A developmental intervention program is prepared for the children and parents. In these cases the psychoneurological development are regularly controlled. The meetings the family are as often as it is possible or necessary in these cases.

The Binet test is rather verbal test of intelligence (not appropriate to recognize the delay of speech-development, but good for measuring problem-solving, vocabulary employment of experience). Early intervention is necessary in the case of delay in expressive speech and difficulties with coordinative movements (danger of difficulties at school!). Learning disability can be diagnosed in the third class earliest. At the age of 8-10 yrs the Binet test can give acceptable information on the intellectual development. If there are more than one problem of different cognitive abilities, that can mean an increased risk from the point of learning disability. These children have problems with mathematics (not with mechanical reading but with the reading comprehension). The number of children with disability was 9 in this small material: reading disability (3), learning disability in mathematics (3) and ADHD (3).

The WISC-IV test was accredited lately, therefore its use started recently. The results of the first 30 tests (the total IQ and especially the quotients for partial abilities: processing speed-, verbal-, performance- and working memory quotients) tend to be weaker corresponding to the international experiences.

The beneficial effect of early start of replacement and the use of higher initial dose is almost generally accepted. Recently 51 articles were analysed publishing IQ values of children with CH. Normal values were detected in one third of the reports but in the other papers the IQ was found significantly lower comparing to controls [80].

The main conclusions: some of the prenatal effects of hypothyroidism may be irreversible especially in the athyroid babies and may be detected subtle, selective deficits of different abilities in the children with CH in comparison to appropriate reference groups [81,82]. Despite these observations the newborns and children with CH may have better psychoneurological development and long-term outcomes without comparison than before the introduction of the screening system.

Recently a very remarkable material was published by Leger and co-workers [83] on long-term health and socio-economic attainment of French young adult (median age: 23,4 yr) patients with permanent CH detected by neonatal screening between 1978 and 1988 on the basis of self-reported data by questionnaires. Round 1200 answers were evaluated and compared to data of controls. Chronic diseases, hearing impairment, visual problems, overweight were found significantly oftener, moreover socio-economic attainment, health-related quality of life, and full-time employment were lower or less among the CH patients. As limitation of the study is given that "outcome data are based on management procedures used early in the history of the CH screening program" (start of therapy, starting dose etc), however 20,6 % of their patients had abnormal serum TSH values (with median of 12,0 mIU/L) determined within 2 yr of the questionnaire study. Therefore one of the author's conclusions is that the patient's care should modify "to improve compliance with treatment and medical care during the transition from pediatric to adult services" [83].

4. Conclusion

In the era before the neonatal thyroid screening 1:4000 incidence of hypothyroidism was calculated in Hungary on the basis of five years (1966-70) survey by questionnaires from pediatricians. The results of TSH screening (413 permanent CH/1,369.503 newborn = 1:3316) confirmed it during the last quarter of a century (1982-2007). The technique and the incidence did not change significantly in this long period.

Transient form of CH was diagnosed in 8,4 % (26/310). Thyroid scintigraphy in 182 cases showed the following results: dysgenesis occurred in 84 % (agenesis 47 %; ectopic lingual 28 %; hypoplasia 9 %), normal-sized eutopic gland ("thyroid in situ") was found in 10 % and enlarged thyroid (dysmorphogenesis) was seen in 6 %.

Thyroid specific genes involved in CH are summarized in a table. In a cohort of 58 patients PAX8 (exon 2 and exon 3) was analysed without deviation. Congenital malformations were detected in 45 cases, and concomitant disorders in 46/210 CH patients.

Score system for predicting CH is proposed using signs (opened posterior fontanel, umbilical hernia, dry skin, enlarged tongue, constipation, laziness, wide nasal bridge and prolonged jaundice) and TSH value.

According to self-experience 10-15 $\mu\text{g}/\text{kg}/\text{day}$ initial dose was administered in the last two decades. Recently L-T₄ and L-T₃ combination was applied in some cases resulting in mostly parallel decrease of elevated TSH and FT₄ level.

The children with CH grow generally in a normal tempo but the disappearance of bone age retardation is individual and may be protracted until 10 years of age. Bone mineral density was measured first by single photon absorptiometry, later by peripheral quantitative computer tomography, what may consider as a more precise method for pediatric use. Children with CH detected by neonatal screening have very slightly decreased total BMD values comparing to controls especially in prepubertal girls, but practically always within the reference range.

The final height of boys was found absolutely comparative with the reference values and the decreasing deviation of the girls did not prove to be significant. The mean menarche age corresponds to the Hungarian reference values in average, but not regarding its distribution. This average derives from the values of two different subgroups characterised with an earlier (< 12 yrs) and with a relative delayed (> 13 yrs) sexual development indicating the relationship between the thyroid and sexual hormone axes.

In the 1980s we observed significant correlation between thyroglobulin levels and IQ values detected lower IQ in athyroidism (Tg < 0,3 ng/ml). We presented ten years ago our experience that the onset of L-T₄ replacement during the first two weeks of life, the initial dose > 10 $\mu\text{g}/\text{kg}/\text{day}$ and the first T₄ level > 3 $\mu\text{g}/\text{dl}$ ensure the best IQ in prepubertal (8,5 \pm 2,5 yrs) children.

In our recent study, using the Wechsler Intelligence Scale for children, it was found, that the partial abilities – especially the performance and working memory – of the adolescents (14-16 yrs) are commonly decreased and the total Wechsler IQ is also tended to the low normal range (93,25 \pm 7,22).

Despite these results the long-term outcomes of the children with CH may consider far better than it was before the neonatal screening.

Finally, a few recent articles are recommended for more up-to-date information [15,53,64,84-88].

Abbreviations

CH - congenital hypothyroidism

TSH - thyroid stimulating hormone

TRH - TSH releasing hormone

TBG- thyroxine binding globulin

DUOX - dual oxidase

T₄ - thyroxine

T₃ - triiodothyronine

FT₄ - free thyroxine

FT₃ - free triiodothyronine

L-T₄ - levothyroxine

L-T₃ - levotriiodothyronine

RIA - RadioImmunoAssay

LIA - Lumino ImmunoAssay

IRMA - ImmunoRadioMetric Assay

DELFLIA - Dissociation-Enhanced Lanthanide Fluorescent ImmunoAssay

ELISA - Enzyme-Linked ImmunoSorbent Assay

CPHD - combined pituitary hormone deficiency

GH - growth hormone

PRL - prolactin

RDS - respiratory distress syndrome

TFT - thyroid function test

PAX8 - paired box 8 (gene)

CNS - central nervous system

GORD - gastro-oesophageal reflux disease

T1DM - type 1 diabetes mellitus

Acknowledgements

We should like to thank L Blatniczky MD, PhD, A Kozma MD and B Tobisch, MD their cooperation during the follow up of these children at the outpatient clinic.

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References

- [1] (Dussault JH, Laberge C. Dosage de la thyroxine (T4) par methode radioimmunologique dans l'eluat de sang deche: nouvelle methode de depistage de l'hypothyroidie neonate. *Union Med Can* 1973;102(10): 2062-2064). 102(10), 2062-2064.
- [2] Klein, A. H, Augustin, A. V, & Foley, T. P. Successful laboratory screening for congenital hypothyroidism. *Lancet* (1974). , 2(7872), 77-79.
- [3] Péter, F, Kovács, L, & Blatniczky, L. Erste Ergebnisse des Nationalprogrammes für Hypothyreose-Screening in Ungarn. *Experiment Clin Endocrinol* (1985). , 86(2), 94-95.
- [4] Mäenpää, J. Congenital hypothyroidism. Aetiological and clinical aspects. *Arch Dis Child* (1972). , 47(12), 914-923.
- [5] De Jonge, G. A. Congenital hypothyroidism in the Netherlands. *Lancet* (1976).
- [6] Alm, J, Larsson, A, & Zetterstrom, R. Congenital hypothyroidism in Sweden. Incidence and age at diagnosis. *Acta Paediatr Scand* (1978).
- [7] Péter, F. Medical care of children with thyroid diseases. (Hungarian) *Magyar Pedia-ter* (1972).
- [8] Harris, K. B, & Pass, K. A. Increase in congenital hypothyroidism in New York State and in the United States. *Mol Genet Metab* (2007). , 91(3), 268-277.
- [9]] Deladoëy, J, Bélanger, N, & Van Vliet, G. Random variability in congenital hypothyroidism from thyroid dysgenesis over 16 years in Quebec. *J Clin Endocrinol Metab* (2007). , 92, 3158-3161.

- [10] Olney, R. S, & Grosse, S. D. Vogt Jr RF. Prevalence of congenital hypothyroidism-current trends and future directions: workshop summary. *Pediatr* (2010). Suppl 2): SS36, 31.
- [11] Hinton CFHHarris KB, Borgfeld L, Drummond_Borg M, Eaton R, Lorey F et al. Trends in incidence rates of congenital hypothyroidism related to select demographic factors: data from the United States, California, Massachusetts, New York, and Texas. *Pediatr* (2010). SS47., 37.
- [12] Mengreli, C, Kanaka-gantenbein, C, Girginoudis, P, Magiakou, M. A, Christakopoulou, I, Giannoulia-karantana, A, et al. Screening for congenital hypothyroidism: the significance of threshold limit in false-negative results. *J Clin Endocrinol Metab* (2010). , 95(9), 4283-4290.
- [13] LaFranchi SHIncreasing incidence of congenital hypothyroidism: some answers, more questions. *J Clin Endocrinol Metab* (2011). , 96(8), 2395-2397.
- [14] Deladoëy, J, Ruel, J, Giguère, Y, & Van Vliet, G. Is the incidence of congenital hypothyroidism increasing? A 20-year retrospective population-based study in Quebec. *J Clin Endocrinol Metab* (2011). , 96(8), 2422-2429.
- [15] Mitchell, M. L, Hsu, H-W, & Sahai, I. and the Massachusetts Pediatric Endocrine Work Group. The increased incidence of congenital hypothyroidism: fact or fancy? *Clin Endocrinol* (2011). , 75(6), 806-810.
- [16] Hertzberg, V, Mei, J, & Therrell, B. L. Effect of laboratory practices on the incidence rate of congenital hypothyroidism. *Pediatrics* (2010). SS53., 48.
- [17] Rapaport, R. Congenital hypothyroidism: an evolving common clinical conundrum. *J Clin Endocrinol Metab* (2010). , 95(9), 4223-4225.
- [18] Olivieri, A, Torreasani, T, Donaldson, M, Krude, H, Van Vliet, G, Polak, M, et al. ESPE consensus meeting on congenital hypothyroidism: main recommendations. (Abstr). *Horm Res* (2012). suppl 1): 38-39.
- [19] Maruo, Y, Takahashi, H, Soeda, I, Nishikura, N, Matsui, K, Ota, Y, et al. Transient congenital hypothyroidism caused by biallelic mutations of the dual oxidase 2 gene in Japanese patients detected by a neonatal screening program. *J Clin Endocrinol Metab* (2008). , 93(11), 4261-4267.
- [20] Hoste, C, Rigutto, S, Van Vliet, G, Miot, F, & De Deken, X. Compound heterozygosity for a novel missense mutation and a partial deletion affecting the catalytic core of the H₂O₂ generating enzyme DUOX2 associated with transient congenital hypothyroidism. *Human Mutation* (2010). E, 1304-1319.
- [21] Péter, F, Blatniczky, L, Kovács, L, & Tar, A. Experience with neonatal screening for congenital hypothyroidism in Hungary. *Endocrinol Experiment* (1989). , 23(3), 143-151.

- [22] Muzsnai, Á. Some aspects for optimalization of hormone substitution in congenital hypothyroidism. (Hungarian) PhD thesis. Budapest, (1991).
- [23] Fujiwara, H, Tatsumi, K, Miki, K, Harada, T, & Miyai, K. Takai S-I et al. Congenital hypothyroidism caused by a mutation in the Na⁺/I⁻ symporter. *Nature Genetics* (1997). , 16(2), 124-125.
- [24] Everett, L. A, Glaser, B, Beck, J. C, Idol, J. R, Buchs, A, Heyman, M, et al. Pendred syndrome is caused by mutations in a putative sulphate transporter gene (PDS) *Nature Genetics* (1997). , 17(4), 411-422.
- [25] Ieiri, T, Cochaux, P, Targovnik, H. M, et al. A 3' splice site mutation in the thyroglobulin gene responsible for congenital goiter with hypothyroidism. *J Clin Invest* (1991). , 88(6), 1901-1905.
- [26] Abramowicz, M. J, Targovnik, H. M, Varela, V, Cochaux, P, Krawiec, L, Pisarev, M. A, et al. Identification of a mutation in the coding sequence of the human thyroid peroxidase gene causing congenital goiter. *J Clin Invest* (1992). , 90(4), 1200-1204.
- [27] Iwatani, N, Mabe, H, Devriendt, K, Kodama, M, & Miike, T. Deletion of NKX2-1 gene encoding thyroid transcription factor-1 in two siblings with hypothyroidism and respiratory failure. *J Pediatr.* (2000). , 137(2), 272-276.
- [28] Hung, W, & Sarlis, N. J. Molecular genetics of thyroid disorders in the neonate: a review. *J Endocr Genetics* (2001). , 2(4), 193-213.
- [29] Krude, H, Schütz, B, Biebermann, H, Von Moers, A, Schnabel, D, Neitzel, H, et al. Choreoathetosis, hypothyroidism, and pulmonary alterations due to human NKX2-1 haploinsufficiency. *J Clin Invest* (2002). , 109(4), 475-480.
- [30] Moreno, J. C, Bikker, H, Kempers, M. J, Van Trotsenburg, A. S, Baas, F, De Vijlder, J. J, et al. Inactivating mutations in the gene for thyroid oxidase 2 (THOX2) and congenital hypothyroidism. *New Engl J Med.* (2002). , 347(2), 95-102.
- [31] Castanet, M, Park, S. M, Smith, A, Bost, M, Léger, J, Lyonnet, S, et al. A novel loss-of-function mutation in TTF-2 is associated with congenital hypothyroidism, thyroid agenesis, and cleft palate. *Human Molec Genetics* (2002). , 11(17), 2051-2059.
- [32] Bans, I, Ansoy, A. E, Smith, A, Agostini, M, Mitchell, C. S, Park, S. M, et al. A novel missense mutation in human TTF-2 (FKHL15) gene associated with congenital hypothyroidism but not athyreosis. *J Clin Endocrinol Metab* (2006). , 91(10), 4183-4187.
- [33] Tonacchera, M, Banco, M. E, & Montanelli, L. Di Cosmo C, Agretti P, De Marco G et al. Genetic analysis of the PAX8 gene in children with congenital hypothyroidism and dysgenetic or eutopic thyroid glands: identification of a novel sequence variant. *Clin Endocrinol* (2007). , 67(1), 34-40.

- [34] Moreno, J. C, & Visser, T. J. New phenotypes in thyroid dysmorphogenesis: Hypothyroidism due to DUOX2 mutations. In: Van Vliet G, Polak M. (eds). *Thyroid gland development and function*. Basel: Karger; (2007). , 99-117.
- [35] Grüters, A. Thyroid hormone transporter defects. In: Van Vliet G, Polak M. (eds). *Thyroid gland development and function*. Basel: Karger; (2007). , 118-126.
- [36] Zamproni, I, Grasberger, H, Cortinovis, F, Vigone, M. C, Chiumello, G, Mora, S, et al. Biallelic inactivation of the dual oxidase maturation factor 2 (DUOX2) gene as a novel cause of congenital hypothyroidism. *J Clin Endocrinol Metab* (2008). , 93(2), 605-610.
- [37] Moreno, J. C, Klootwijk, W, Van Toor, H, Pinto, G, Alessandro, D, & Lèger, M. A et al. Mutations in the iodotyrosine deiodinase gene and hypothyroidism. *New Engl J Med* (2008). , 358(17), 1811-1818.
- [38] Afink, G, Kulik, W, Overmars, H, De Randamie, J, Veenboer, T, Van Cruchten, A, et al. Molecular characterization of iodotyrosine dehalogenase deficiency in patients with hypothyroidism. *J Clin Endocrinol Metab* (2008). , 93(12), 4894-4901.
- [39] Huler, I, Hermanns, P, Nestoris, C, Heger, S, Refetoff, S, Pohlenz, J, et al. A single copy of the recently identified dual oxidase maturation factor (DUOX) 1 gene produces only mild transient hypothyroidism in a patient with a novel biallelic DUOX2 mutation and monoallelic DUOX1 deletion. *J Clin Endocrinol Metab* (2011). E, 841-845.
- [40] Muzsnai, A, Csókay, B, & Péter, F. Thyroid function, associated malformations, gene alterations and its importance in congenital hypothyroidism. In: Péter F. (ed). *Progress in paediatric endocrinology*. Budapest: Science Press Ltd; (2008). , 88-91.
- [41] Park, S. M. Chatterjee VKK. Genetics of congenital hypothyroidism. *J Med Genetics* (2005). , 42(5), 379-389.
- [42] Péter, F, & Muzsnai, A. Congenital disorders of the thyroid: hypo/hyper. *Endocrinol Metab Clin N Am* (2009). , 38(3), 491-507.
- [43] Germak, J. A. Foley Jr TP. Longitudinal assessment of L-thyroxine therapy for congenital hypothyroidism. *J Pediatr* (1990). , 117(2), 211-219.
- [44] Fisher, D. A. Management of congenital hypothyroidism. *J Clin Endocrinol Metab* (1991). , 72(3), 380-386.
- [45] Rovet, J. F, & Ehrlich, R. M. Long-term effects of L-thyroxine therapy for congenital hypothyroidism. *J Pediatr* (1995). , 126(3), 380-386.
- [46] Bargagna, S, Canepa, G, Cossagli, C, et al. Neuropsychological follow-up in early-treated congenital hypothyroidism: a problem-oriented approach. *Thyroid* (2000). , 10(3), 243-249.
- [47] Bongers-schokking, J. J, Koot, H. M, Wiersma, D, & Verkerk, P. H. de Muinck Keizer-Schrama SMPF. Influence of timing and dose of thyroid hormone replacement on de-

- velopment in infants with congenital hypothyroidism. *J Pediatr* (2000). , 136(3), 292-297.
- [48] Hindmarsh, P. C. Optimisation of thyroxine dose in congenital hypothyroidism. *Arch Dis Child* (2002). , 86(2), 73-75.
- [49] Kempers MJEvan der Sluijs Veer L, Nijhuis-van der Sanden et al. Intellectual and motor development of young adults with congenital hypothyroidism diagnosed by neonatal screening. *J Clin Endocrinol Metab* (2006). , 91(2), 418-424.
- [50] Péter, F, Blatniczky, L, & Breyer, H. About the form and replacement dose of thyroid hormones in the treatment of congenital hypothyroidism (CH). In: Delange F, Fisher DA, Glinioer D (eds). *Research in congenital hypothyroidism*. New York and London, Plenum Press. (1989). , 338.
- [51] Jones, J. H, Gellén, B, Paterson, W. F, Beaton, S, & Donaldson, M. D. Effect of high versus low initial doses of L-thyroxin for congenital hypothyroidism on thyroid function and somatic growth. *Arch Dis Child* (2008). , 93(11), 940-944.
- [52] Balhara, B, Misra, M, & Levitsky, L. L. Clinical monitoring guidelines for congenital hypothyroidism: laboratory outcome data in the first year of life. *J Pediatr* (2011). , 158(4), 532-537.
- [53] LaFranchi SH Approach to the diagnosis and treatment of neonatal hypothyroidism. *J Clin Endocrinol Metab* (2011). , 96(10), 2959-2967.
- [54] Kemper, A. R, Ouyang, L, & Grosse, S. D. Discontinuation of thyroid hormone treatment among children in the United States with congenital hypothyroidism: findings from health insurance claims data. *BMC Pediatrics* (2010).
- [55] Korzeniewski, S. J, Grigorescu, V, Kleyn, M, Young, W. I, Birbeck, G, Todem, D, et al. Transient Hypothyroidism at Year Follow-Up among Cases of Congenital Hypothyroidism Detected by Newborn Screening. *J Pediatr*. (2012). Aug 7. [Epub ahead of print], 3.
- [56] Hennemann, G, Docter, R, Visser, T. J, Postema, P. T, & Krenning, E. P. Thyroxine plus low-dose, slow-release triiodothyronine replacement in hypothyroidism: proof of principle. *Thyroid* (2004). , 14(4), 271-275.
- [57] Gullo, D, Latina, A, & Frasca, F. Le Moli R, Pellegriti G, Vigneri R. Levothyroxine monotherapy cannot guarantee euthyroidism in all athyreotic patients. *PloS One*. (2011). e22552
- [58] Biondi, B, & Wartofsky, L. Combination treatment with T₄ and T₃: toward personalized replacement therapy in hypothyroidism? *J Clin Endocrinol Metab* (2012). , 97(7), 2256-2271.

- [59] Wiersinga, W. M, Duntas, L, Fadeyev, V, & Nygaard, B. Vanderpump MPJ. 2012 ETA guiderlines: the use of L-T4 + L-T3 in the treatment of hypothyroidism. *Eur Thyroid J* (2012). , 1, 55-71.
- [60] Eiben, O, & Pantó, E. The Hungarian National Growth Standards. *Antrop Kőzl* (1986). , 30(1), 5-23.
- [61] Greulich, W. W, & Pyle, S. I. Radiographic atlas of skeletal development on hand and wrist. 2nd ed. Stanford, University Press, (1959).
- [62] Péter, F, Muzsnai, Á, & Kántor, I. Thyroid hormones and bone mineralization in children and adolescents. In: Schönau E, Matkovic V (eds). *Paediatric osteology. Prevention of osteoporosis- a paediatric task?* Amsterdam etc, Elsevier, (1998). , 183-189.
- [63] Péter, F, Muzsnai, Á, & Gyimes, J. Nation-wide survey for normal values of BMD in children measured by mobil pQCT. (Abstr) *Horm Res* (2002). suppl 2): 80.
- [64] Bucher, H, Prader, A, & Illig, R. Head circumference, height, bone age and weight in 103 children with congenital hypothyroidism before and during thyroid hormone replacement. *Helv Paediatr Acta* (1985). , 40, 305-316.
- [65] Grant, D. B. Growth in early treated congenital hypothyroidism. *Arch Dis Child* (1994). , 70(6), 464-468.
- [66] Dickerman, Z, & De Vries, L. Prepubertal and pubertal growth, timing and duration of puberty and attained adult height in patients with congenital hypothyroidism (CH) detected by the neonatal screening programme for CH- a longitudinal study. *Clin Endocrinol (Oxf)* (1997). , 47(6), 649-654.
- [67] Adachi, M, Asakura, Y, & Tachibana, K. Final height and pubertal growth in Japanese patients with congenital hypothyroidism detected by neonatal screening. *Acta Paediatr* (2003). , 92(6), 698-703.
- [68] Salerno, M, & Micillo, M. Di Maio S, Capalbo D, Ferri P, Lettierio T et al. Longitudinal growth, sexual maturation and final height in patients with congenital hypothyroidism detected by neonatal screening. *Europ J Endocrinol* (2001). , 145(4), 377-383.
- [69] Soliman, A. T, Azzam, S, Elawwa, A, Saleem, W, & Sabt, A. Linear growth and neurodevelopmental outcome of children with congenital hypothyroidism detected by neonatal screening: a controlled study. *Indian J Endocrinol Metab* (2012). , 16(4), 565-568.
- [70] Radetti, G, Castellan, C, Tató, L, Platter, K, Gentili, L, & Adami, S. Bone mineral density in children and adolescent females treated with high doses of L-thyroxine. *Horm Res* (1993). , 39(1), 127-131.
- [71] Saggese, G, Bertelloni, S, Baroncelli, G. I, Costa, S, & Ceccarelli, C. Bone mineral density in adolescent females treated with L-thyroxine: a longitudinal study. *Eur J Paediatr* (1996). , 155(8), 452-457.

- [72] Leger, J, Ruiz, J. C, Guibourdenche, J, Kindermans, C, Garabedian, M, & Czernichow, P. Bone mineral density and metabolism in children with congenital hypothyroidism after prolonged L-thyroxine therapy. *Acta Paediatr* (1997). , 86(7), 704-10.
- [73] Salerno, M, & Lettiero, T. Esposito-del Puente A, Esposito V, Capalbo D, Carpinelli A et al. Effect of long-term l-thyroxine treatment on bone mineral density in young adults with congenital hypothyroidism. *Eur J Endocrinol* (2004). , 151(6), 689-694.
- [74] Kempers, M. J, Vulsma, T, Wiedijk, B. M, De Vijlder, J. J, Van Eck-smit, B. L, & Verberne, H. J. The effect of life-long thyroxine treatment and physical activity on bone mineral density in young adult women with congenital hypothyroidism. *J Pediatr Endocrinol Metab* (2006). , 19(12), 1405-1412.
- [75] Rovet, J, Ehrlich, R, & Sorbara, D. Intellectual outcome in children with fetal hypothyroidism. *J Pediatr* (1987). , 110(5), 700-704.
- [76] Glorieux, I, Desjardins, M, Letarte, J, Morissette, J, & Dussault, J. H. Useful parameters to predict the eventual mental outcome of hypothyroid children. *Pediatr Res* (1988). , 24, 6-8.
- [77] Peter, F, Muzsnai, A, & Szigervari, A. Intellectual assessment of hypothyroid children detected by screening. *Acta Med Austr* (1992). Sonderheft 1): 60-61.
- [78] Gráf-kucsera, R, Péter, F, & Muzsnai, Á. Intellectual development of children with congenital hypothyroidism (CH) detected by newborn screening. In Morreale de Escobar G, de Vijlder JJM, Butz S, Hostalek U (editors) *The thyroid and brain*. Stuttgart, New York. Schattauer, (2003). , 310-311.
- [79] Péter, F, Gráf, R, Blatniczky, L, & Muzsnai, Á. Neuropsychological development of children with congenital hypothyroidism recognized by neonatal screening. (Abstr) *Pediatr Res* (2001). Suppl 2): 158A.
- [80] LaFranchi SHAustin J. How should we be treating children with congenital hypothyroidism? *J Pediatr Endocrinol Metab* (2007). , 20(5), 559-578.
- [81] Oerbeck, B, Sundet, K, Kase, B. F, & Heyerdahl, S. Congenital hypothyroidism: influence of disease severity and L-thyroxine treatment on intellectual, motor, and school-associated outcome in young adults. *Pediatrics* (2003). , 112(4), 923-930.
- [82] Zoeller, R. T, & Rovet, J. Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings. *J Neuroendocrinol* (2004). , 16(10), 809-818.
- [83] Leger, J, Ecosse, E, Roussey, M, Lanoë, J. L, Larroque, B, et al. Subtle health impairment and socioeducational attainment in young adult patients with congenital hypothyroidism diagnosed by neonatal screening: a longitudinal population-based cohort study. *J Clin Endocrinol Metab* (2011). , 96(6), 1771-1782.

- [84] Rastogi, M. V. LaFranchi SH. Congenital hypothyroidism. *Orphanet J Rare Dis* (2010). , 5(17), 1-22.
- [85] Rajput, R, Chatterjee, S, & Rajput, M. Can levothyroxine be taken as evening dose? Comparative evaluation of morning versus evening dose of levothyroxine in treatment of hypothyroidism. *J Thyroid Res* (2011). Article ID 505239, 5 pages doi: 10.4061/2011/505239., 2011
- [86] Péter, F, & Muzsnai, Á. Congenital disorders of the thyroid: hypo/hyper. *Pediatr Clin N Am* (2011). , 58(5), 1099-1115.
- [87] Taylor, P. N, Panicker, V, Sayers, A, Shields, B, Iqbal, A, Bremner, A, et al. A meta-analysis of the associations between common variation in the PDE8B gene and thyroid hormone parameters, including assessment of longitudinal stability of associations over time and effect of thyroid hormone replacement. *Eur J Endocrinol* (2011). , 164(5), 773-780.
- [88] Wheeler, S. M, Willoughby, K. A, Mcandrews, M. P, & Rovet, J. F. Hippocampal size and memory functioning in children and adolescents with congenital hypothyroidism. *J Clin Endocrinol Metab* (2011). E, 1427-34.

