ANALYSIS OF PHYSICAL AND MENTAL DEVELOPMENT OF CHILDREN WITH APLASIA, HYPOPLASIA AND ECTOPY OF THE THYROID GLAND

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Objective. Evaluation of clinical and biochemical differences between various forms of thyroid dysgenesia in children.

Methods. The study involved 102 children at the age between 4.8 and 14.2 years who were born with congenital hypothyroidism (CH), as diagnosed by neonatal screening examinations. In all the children diagnosis was settled and the levothyroxine (L-T_4) administration was started by the 19th day of life. Out of the examined children, 79 were selected with following three forms of developmental thyroid disorders: Group I – athyroidism (thyroid aplasia or agenesis), Group II – thyroid hypoplasia, Group III – thyroid ectopy. On the basis of neonatal TSH (nTSH) levels obtained by screening and serum TSH, FT_4 and Tg concentrations, the severity of hypothyroidism was determined at the time of diagnosis. Physical and mental development of the children was evaluated on the basis of growth and bone age indices and Wechsler's scale, respectively.

Results. Developmental disorders were diagnosed in 79 cases (77.4 % CH) which included 45 cases (44.1%) of athyroidism, 31 cases (30.4%) of thyroid hypoplasia and 3 cases (2.9%) of thyroid ectopy. The physical and mental development in the studied groups was evaluated as normal.

Conclusions: In the group of children with athyroidism, significantly lower growth indices and IQ values were found in comparison with respective values observed in the other study groups. However, the indices of physical and mental development in all the studied groups were within the normal values for children population. An early diagnosis and early administration of hormonal replacement therapy by L-T_4 ensure normal development of children with CH, regardless of underlying causes and associated with them severity of congenital hypothyroidism.

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Key words: Thyroid aplasia – Thyroid hypoplasia – Thyroid ectopy – Physical and mental development – *TSHR* gene – Transcription factors

Thyroid hormones control the normal course of metabolic processes, responsible for the normal physical and mental development of foetus and neonate. Congenital hypothyroidism (CH) is the most frequent congenital endocrinopathy – its average incidence is 1:4000 deliveries. About 120 children per year are born in Poland with risk of CH-related disorders in physical and mental development.

Developmental disorders of the thyroid gland (agenesis, hypoplasia, ectopy and extrathyroid aberrations) stand – according to various authors – for 75 % to 93 % of all CH cases (BAKKER et al. 2000; KRUDE et al. 2000). These disorders occur already on about the 16th and 17th day of the embryonal period. Primordium of the thyroid gland develops in the pharyngeal floor, between the 1st and 2nd pair of branchial clefts and descends

down the neck along the thyroglossal duct. On the 7th week of intrauterine life, the thyroid primordium reaches the lower section of the neck; its upper segment undergoes involution, while in the lower segment characteristic elements of the thyroid gland develop. On the 8th week of intrauterine life, the thyroid presents with iodine uptake abilities and, on the 10th week – the potential of iodothyronine production develops. The lack of primordial development, disturbed translocation to the lower cervical section and/or formation of extrathyroid aberrations of thyroid tissue provide a possibility for developmental anomalies of the thyroid gland, which lead to deficient hormonal function.

Developmental disorders include: total lack of the thyroid gland (athyroidism), thyroid hypoplasia and ectopic thyroid location. Until not long ago, it had been assumed that developmental disorders of the thyroid gland were sporadic in character.

At present, the participation of following genetic factors has been shown in the pathogenesis of developmental thyroid disorders: thyrotropin-stimulating hormone receptor gene (*TSHR*), paired box gene 8 (*PAX8*) and thyroid transcription factor 1 and 2 genes (*TTF1, TTF2).*

Thyrotropin receptor defect may result in no reaction of the receptor following binding structurally and functionally normal TSH molecule, the consequence being an abnormal development and structure of the thyroid gland (Postiglione et al. 2002) and decreased expression of genes, associated with iodine metabolism, i.e., thyroid peroxidase (*TPO*) and sodium iodide symporter (*NIS*) genes. Disturbances in the process of adenyl cyclase activation and a considerable decrease of cAMP content, following inactivating mutation of *TSHR* gene have been observed (Tonacchera et al. 2000). Clinically, a child affected by the above mentioned abnormality, is born with congenital thyroid hypoplasia and CH.

Thyrotropin receptor gene was identified in 1989 in the long arm of chromosome 14 (14q). More than 20 TSHR function inactivating mutations have been described so far, including *missense* and *nonsense* mutations, correlated with moderately or strongly expressed clinical symptoms (Park and Chatterjee 2005).

Studies in mice have revealed the existence of TTF1, TTF2 and PAX8 transcription factors, undergoing expression in tissue of developing thyroid gland and influencing the differentiation, migration and initiation of the secretory function of this gland. Mutations of genes of these factors either neutralize or change their ability to bind with DNA, depriving them of the most important function, i.e., regulation of transcription processes.

Thyroid transcription factor 1 is an early marker of thyroid cell differentiation, necessary for the normal development and proliferation of follicular cell precursors, taking also part in the control of thyroglobulin (*Tg*), *TPO* and *TSHR* genes; *TTF1* encoding gene is localized in the long arm of chromosome 14 (14q13), it is 3.3 kb long and consists of two (2) exons and one (1) intron. Mutation in this gene may result in athyroidism, as well as in hypoplasia and/or thyroid ectopy (Park and Chatterjee 2005). Point mutations have been described with accompanying choreoathetosis, muscular hypotonia and changes in the lungs (Breedveld et al. 2002). Also, mutation of the TTF1 factor was described, leading to suppression of *Tg* gene expression, resulting in congenital goitre with hypothyroidism (Acebron et al. 1995). However, in studies undertaken in a large group of patients, no mutation of *TTF1* gene was observed (Lapi et al. 1997; Perna et al. 1997).

The TTF2, also called thyroid nuclear factor 2 (TNF2), undergoes expression in the embryonic period. It is responsible for normal thyroid development and for the process of thyroid gland migration along the thyroglossal duct, it also influences the expression of Tg and TPO. The *TTF2* gene is localised in the long arm of chromosome 9 (9q22) and consists of one exon. The expression of this gene is present in the thyroid, the pituitary, the intestinal endoderm and craniopharyngeal ectoderm, forming Rathke's pocket and the palate (Perna et al. 1997). In humans, point mutations have been found within the *TTF2* gene. Point mutations have been described, which resulted in athyroidism, cleft palate, atresia of posterior nares and cleft glottis in homozygotes (Castanet et al. 2002).

The PAX8 factor is a protein necessary for normal thyroid development during foetal life; it also has effects on the maturation and proliferation of thyroid follicular cells, it also activates transcriptions of *TPO* and *Tg*, *TSHR* genes and the cAMP-dependent transcription of the *NIS* gene (Park and Chatterjee 2005). PAX8 factor participates also in the regulation of expression of the proteins, which play a key role in the biosynthesis and metabolism of thyroid hormones.

The *PAX8* gene is localised in the long arm of chromosome 2 (2q12-14). Its expression is found in the thyroid, the kidneys and the brain (Meeus et al. 2004; Park and Chatterjee 2005). A defect of the *PAX8* gene may bring about athyroidism or thyroid hypoplasia with

hypothyroidism of various severity. Dominant autosomal mutations of the *PAX8* gene (of *missense* and R108 stop type) have been found in patients with ectopy and with different degrees of thyroid hypoplasia or ectopy (CONGDON et al. 2001).

Early diagnosis of CH and early administration of replacement therapy is dramatically important from the point of view of child development. A detailed diagnosis of CH underlying cause may constitute the background for further molecular studies of CH. Therefore, the goal of the reported study has been a clinical and biochemical evaluation of patients with CH, allowing for the diagnosis of thyroid development disorders, and an assessment of physical and mental development of examined patients, depending on the type of recognised defect.

Material and Methods

The study involved 102 children at the age between 4.8 and 14.2 years (78 girls and 24 boys), all of them being patients of the our Department and of the Outpatient Clinic of Paediatric Endocrinology of the Polish Mother's Memorial Hospital – Research Institute because of CH diagnosed in the neonatal period. In all the children, diagnosis was settled and the levothyroxine (L-T_4) administration was started between the 9th and the 19th day of life. The applied principles of therapy and monitoring were those, defined the Study Group for Congenital Hypothyroidism of the European Society for Paediatric Endocrinology, ESPE (GRUTERS et al., 1994; TOUBLANC et al., 1999).

The examination included in the present study was performed after a 28 days of L-T_4 withdrawal period. The diagnosis of developmental thyroid disorders in those patients was based on the following tests: 1. serum concentrations of TSH, free thyroxine (FT_4), thyroglobulin (Tg), antibodies against thyroperoxidase (TPOAB), against thyroglobulin (TgAb) (ECLIA, Roche) and against TSH receptor (TRAb) (RIA, BRAHMS); 2. ultrasound imaging of the neck and of the sublingual region; 3. neck scintigraphy with ^{131}I (the total activity: 0.5 μCi/kg b.w., maximal activity – 20 μCi); 4. radioiodine uptake ability of the thyroid gland, measured after 24 hours from ^{131}I administration. On the basis of these examinations, the patients were divided into three groups: I – with athyroidism, II – with thyroid hypoplasia, III – with ectopy of the gland.

In the studied groups, a retrospective evaluation of thyroid functions was performed, regarding the moment of CH diagnosis during the first days of life, and analysing the following parameters: the concentration of neonatal TSH (nTSH) obtained by neonatal screening examination and serum concentrations of TSH, FT_4 and Tg, where measured at recall, few days after screening data (between the 9th and the 19th day of life).

The physical development of examined children was analysed on the basis of birth weight and growth indices. Because of different age and sex of the examined children, the height standard deviation score (HSDS), was calculated for the calendar age (CA) and sex of all the patients, as well as the standard deviation score of the target height (THSDS) – following the SDS of parents' height and the value of the, so-called, corrected HSDS (corrHSDS = HSDS – THSDS). In all the children, bone age was evaluated, comparing it with the calendar age (BA – CA).

The evaluation of mental development was performed, using Wechsler's intelligence scale. The distribution of intelligence quotient (IQ) was as follows: 115-85 pts – average intelligence, 84-70 pts – lower than average intelligence, 69-55 pts – mild mental impairment, 39-26 pts – considerable mental impairment, 25 pts and below – deep mental impairment.

The patients with mental disorders and their families were qualified to molecular studies (JEZIOROWSKA et al., in press).

Statistical analysis was performed by means of the STATISTICA 5.1 PL program. Student's t-test was used for non-correlated variables. Differences were regarded as statistically significant when $p < 0.05$.

Results

Developmental disorders were diagnosed in seventy-nine (79) cases, i.e., in 77.4% of the studied cases, including athyroidism – forty-five (45) cases (44.1%), thyroid hypoplasia – thirty-one (31) cases (30.4%) and thyroid ectopy – three (3) cases (2.9%).

The data on thyroid function at the time of first CH diagnosis in neonates (Table 1) showed significant differences between the studied groups. Thus, in the group of children with athyroidism, significantly higher serum concentrations of nTSH and TSH and the lowest serum concentration of FT_4 (0.19 ng/dL) were found, the latter combined with decreased Tg concentrations, when compared to respective values in the group of children with thyroid hypoplasia and ectopy. However, the average birth weight did not significantly differ among the studied groups.

Table 1
Evaluation of thyroid function, performed at the time of thyroid dysgenesia diagnosis in the studied groups

Group	Type of the defect		Birth weight (g)	nTSH (mIU/L)	TSH (mIU/L)	FT_4 (ng/dL)	Tg (ng/mL)
I	Athyroidism						
(n-45)		mean	3148±831	234.6[c] ± 45.6	147.8[b]±32.9	0.19[a]±0.03	1.1[a]±3.9
		range	2314- 3985	(182.3 – 287.9)	(87.6 –212.3)	(0.12 – 0.32)	(0.2 – 5.6)
II	Hypoplasia						
(n-31)		mean	3209±672	134.6[c]±29.8	67.8[b]±23.2	0.39[a]±0.12	12.3[d]±5.1
		range	2543- 3890	(98.7 – 178.5)	(34.5 – 112.3)	(0.25 – 0.49)	(6.8 – 23.4)
III	Ectopy						
(n-3)		mean	3026±763	87.6±23.9	39.7±12.8	0.40±0.1	9.8±2.9
		range	2254- 3798	(54.3 – 99.0)	(23.1 – 45.2)	(0.32 – 0.54)	(7.5 – 12.3)

The values in columns, marked with the same letters, significantly differ between each other; n – number of cases; p – the level of significance; a, b, c – $p<0.01$; d – $p<0.05$

Table 2
Evaluation of the physical development of children with thyroid dysgenesia performed in the studied groups

Group	Type of defect		HSDS	THSDS	CorrHSDS	BA – CA* (months)
I	Athyroidism					
(n = 45)		mean	-0.34[a]	0.87	-1.21[b]	-7.15[c]
		range	(-1.78 – 1.23)	(-1.0 – 1.35)	(-1.59 – 1.12)	[-18 – (+3)]
II	Hypoplasia					
(n = 31)		mean	0.89[a]	0.62	0.28[b]	1.00[c]
		range	(1.12 – 1.67)	(-0.5 – 1.27)	(-0.9 – 1.40)	[-12 – (+8)]
III	Ectopy					
(n = 3)		mean	0.76	-0.02	0.79	+3.30
		range	(0.34 – 1.1)	(-0.9 – 0.88)	(0.39 – 1.24)	[-12 – (+10)]

The values in columns, marked with the same letters, significantly differ between each other; n – number of cases; p – the level of significance; a. b – $p<0.05$, c – $p<0.01$
* Difference between BA and CA, expressed in months

The analysis of physical development of the examined children with particular developmental anomalies of the thyroid gland (Table 2) did not reveal growth disturbances in any of the groups, despite the differentiated severity of hypothyroidism at the time of diagnosis. The lowest HSDS value was found in the group with athyroidism; the HSDS index significantly differed in that group from either THSDS or corrHSDS. However, that group was heterogenous – HSDS values ranged from -1.78 to 1.23. The growth indices – HSDS and corr HSDS – in the group with athyroidism differed significantly from the same indices in the group with thyroid hypoplasia. The group with thyroid ectopy was represented by three (3) patients only – it may be concluded that such a small number of patients was at the basis of statistically insignificant differences. No bone age retardation (characteristic symptom for CH) was observed – the actual bone age delay (the difference between bone age and calendar age) was 3.8 months in the whole group. In case of athyroidism, bone age delay vs. the calendar age was -7.15 months. In the group with thyroid hypoplasia, tendencies towards slight acceleration of the bone age (a 3.3-month acceleration in the bone age were found).

The results of mental development evaluation, performed in the studied groups, are presented in Table 3. The intelligence quotient (IQ) of all the examined children with CH was either within the average or lower than average intelligence, while in 5 cases, it was above the average intelligence level (IQ within 70-128 pts, the mean value – 101 pts). In case of the children with athyroidism, the mean IQ was significantly different from the IQ in the group of children with thyroid hypoplasia, being within the lower values of the average intelligence; in five (5) patients, intelligence was lower than average, while two children demonstrated intelligence above the average level.

Table 3
Evaluation of mental development in children, performed in the studied groups

Group	Type of CH defect	IQ (mean; range)
I (n = 45)	Athyroidism	87[a] (76 – 123)
II (n = 31)	Hypoplasia	103[a] (112 – 72)
III (n = 3)	Ectopy	112 (109 – 121)

The values in columns, marked with the same letters, significantly differ between each other; n – number of cases; p- the level of significance; IQ – intelligence quotient; a – $p<0,05$

Discussion

Among the investigated children the incidence of developmental thyroid disorders was concordant with the data published by others (Bakker et al. 2000; Krude et al. 2000; Jackson and Cobb 1986; Wang and Crapo 1997). However, the incidence of thyroid ectopy in the examined children with CH was considerably lower when compared to the data of others (Krude et al. 2000; Medeiros-Neto and Stanbury 1994), e.g. 2 % vs. 45 %, respectively. It is known that the normal thyroid hormone levels are required for the proper development of the nervous system, especially during the intrauterine period and first years of life. Thyroid hormones of the mother (in the initial period) and of foetus (from the 12th week of foetal life) influence all the developmental transformations in the brain, such as growth processes, maturation, neuron and glia cell migrations (Vulsma et al. 1989). In turn, thyroid hormones, by controlling the expression of a number of genes, take a part in the development of the cytoskeleton, processes, synapses an the myelin sheath of neurons. They are also a necessary component for the physiological growth of a young organism, stimulating the growth hormone (GH) secretion and also the secretion of the insulin-like growth factor (IGF-I) and the development of the growth cartilage (Wasniewska et al. 2003). Although thyroid hormones do not seem to play any important role in the general foetal growth process (Wasniewska et al. 2003), the bone age retardation as observed in neonates with severe forms of CH may prove thyroid hormone participation in somatic development already during the foetal period. In this case perhaps the direct stimulation of IGF-I synthesis by T_3 in osteoblasts is of some importance (Brook 1995).

It is known that athyroidism is the most severe form of CH and a number of authors report abnormal development of children with athyroidism, both physical and mental, despite early administered and properly managed treatment (Alvarez et al. 2004; Jackson and Cobb 1986; Morin et al. 2002; Wasniewska et al. 2001).

Some authors assume that, in contrast to disorders of CNS which may be reversible only to a certain degree (Chan and Kilby 2000), during the replacement treatment of CH by thyroxine the general growth normalisation is advancing (Heyerdahl et al. 1997). Dickerman and De Vries (1997) demonstrated that the growth of children which were treated during the initial 6 months during puberty with a large dose of L-T4, correlated with the growth of their parents.

In the examined group, the HSDS index of patients with athyroidism was normal, when referred to the general children population, however, the mean growth of those children was significantly lower from the anticipated growth (HSDS < THSDS; values: -0,34 vs. 0.87, respectively, see Table 2) and, consequently, also from corrHSDS (HSDS < corrHSDS; values: -0.34 vs. 1.21, respectively, see Table 2). That means, that even the optimally treated patients with athyroidism are characterized by the limited growth potential. In the case of children with thyroid hypoplasia or ectopy, the mean growth of those patients was above the mean value for the population and higher from THSDS.

The intelligence quotient of the children with athyroidism significantly differed from that in other groups thus supporting the views about irreversible changes in the CNS, observed in severe hypothyroidism (Fuggle et al. 1991). However, considering the fact that intelligence distribution in standardisation studies is close to theoretical distribution (what means that about 95 % of the population has IQ within the range of 70 – 130 pts)

(Kresiner et al. 2004; Fuggle et al. 1991), all the children with CH, including those with athyroidism, did not significantly differ from the general children population.

Fuggle et al. (1991) showed that the onset of therapy at the age of 1 month does not yet give any possibility to fully compensate the psychoneurological development of children with CH, especially those with severe form of hypothyroidism. Thus, it was concluded that the technique and efficiency of screening tests should be improved to enable the substitution treatment before the 2nd week of life (Gruters et al. 1994; Toublanc et al. 1999).

It should be stressed that in the examined group the treatment was started on the 19th day of life, the initial dose of L-T_4 being considerably large (10-15 μg/kg b.w.). Later, the effects of treatment was monitored by the estimation of TSH and FT_4 serum levels thus attempting to maintain the FT_4 level within the upper half of the reference range and that of TSH within a normal range (according to the ESPE's recommendations; Gruters et al. 1994).

Klein et al. (1976) stated that the children with a mean value of T_4 level during first 2 years of treatment showed significantly lower IQ in word scale at the age of 6 than the children with T_4 concentration of 12 – 14 μg/dl. Kreisner et al. (2004) showed the dependence of the degree of mental impairment on T_4 concentration, the time of treatment onset but, first of all, on the number of visits during the first year of treatment, i.e., on the regularity of treatment.

The analysis of gene mutations in our children resulted in the identification of a new, so far not described mutation, inactivating the TSH receptor in exon 10 of the *TSHR* gene. It consists on transversion of cytosine (C) in 1431 into guanine (G). The change of C → G is a *nonsense* mutation resulting in the conversion of normally present tyrosine (Y) in codon 444 (TAC) into stop (X) codon (Y444X) (Jeziorowska et al., in print); twenty four (24) children (and the members of their families) with thyroid dysgenesia were included in that study; only one (1) *TSHR* gene mutation in the affected girl and her healthy sister – as mentioned above – was demonstrated, it was a novel mutation (Jeziorowska et al., in print).

Summing up, in the group of children with athyroidism, significantly lower growth indices and IQ were found, in comparison with the other studied groups. Despite the statistically significant differences in the studied groups, the indices of physical and mental development of children with CH did not differ from standards for the child population which includes also the group with the most severe form of CH – athyroidism. On the basis of these findings, it may be stated that the early diagnosis and properly managed treatment are most important for the development of children with CH. Thus, aiming at CH treatment optimisation is the most important task for paediatric endocrinologists.

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