Incidence of primary congenital hypothyroidism and relationship between diagnostic categories and associated malformations

"Increased incidence of primary Congenital Hypothyroidism (CH) and the influence in the etiology and associated malformations"

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INTRODUCTION

Congenital hypothyroidism (CH), the thyroid hormone deficiency since birth, is the most common congenital endocrine disease, which can lead to severe neuropsychomotor development delay and growth failure if not treated promptly (A, B, D). The incidence of CH has been indicated as 1:3000-4000 births but is influenced by the neonatal screening strategy performed in each country (NJ, RR, BB). In the last decades the incidence of this condition has grown progressively and the main reasons for this increase are related to the reduction of the limit level of thyroid-stimulating hormone (TSH) in the neonatal screening strategy and to a higher rate of risk factors for a newborn to develop a CH.

Actually, in Italy each Region has adopted a different neonatal screening strategy; in the Piedmont Region in recent years the cut-off limit for TSH on dried blood spots (DBS) has been progressively lowered to the current levels of 8 μIU / ml at the first screening (at 48 hours of life) and 6.5 μIU/ml at the second one, performed 7-15 days after the first screening, if pathological. On the other hand, over the years, newborns born from preterm delivery or multiple pregnancy, at risk for CH, are increasing (P, S, RS, VZ, WW). Other factors that can influence the incidence of CH include the current changes in population ethnicities, the demographics of the screened population, the iodine deficiency in the diet, the presence of genetic alterations in genes responsible for thyroid ontogenesis or function or syndromes associated with CH (II,KK;JJ). The main genes known so far involved in thyroid development are *NKX2-1, FOXE1, PAX8, NKX2-5, GLIS3, JAG1, TBX1, NTNT1* and *CDCA8,* responsible for the gland dysgenesis when mutated, and *TSHR, GNAS, SLC5A5, SCL26A4, DUOX1/2, DUOAXA2, TPO, TG, IYD/DEHAL* associated with thyroid dyshormonogenesis (A, B, C, E, J, TH, AB, CD, ËF, IJ, PQ, OO, PP). Thyroid dysgenesis, classified as total agenesis, ectopic (single or dual foci) and hemiagenesis or hypoplasia, is responsible for 75-85 % of all cases of CH (A, H). The most common diagnostic category is the ectopic gland, identified in up to 80% of cases with thyroid dysgenesis, while agenesis and

hypoplasia occur in 20-30% and 5% of cases, respectively (C, E, G, N). Thyroid dyshormonogenesis was classically reported in 15-25% of cases, but in the last years the incidence of CH caused by the in situ thyroid gland dyshormonogenesis has increased to 40-50% (A, Ë).

The definitive diagnosis of CH requires biochemical assessment of thyroid function by TSH, fT4, fT3 and thyroglobulin measurement, radiological evaluation through Tc^{99} pernectate or I^{123} scintigraphy and ultrasound assessment to confirm gland agenesis (EE, GG, AA, NO, L, O, V, Y, Z, SH, GH, K). Once diagnosed, the substitutive treatment with l-thyroxine has to be started as soon as possible at 10-15 μg/kg/d dosage, especially when s-TSH is above 20 μUI/ml (F, I, M, Q, R, GJ, LL, ZH, TU, CC).

Since the late 1980s, a high prevalence of congenital anomalies associated with CH has been reported [AAA, BBB, CCC, DDD, EEE, FFF, GGG, QQQ, DH]. The main malformations, reported from 10.5% to 59% of all newborns with CH, are cardiac defects, cleft palate and/or cleft lip, abnormalities of the urogenital, gastrointestinal and musculoskeletal system, as well as chromosomal abnormalities. The most frequently affected system is the cardiovascular system. Congenital heart disease (CHD) has been observed in 4.9-14% up to 50% of all newborns with CH (U, T, Ç, W, ZZ, LM, TT, QQ). A higher rate of other morphological abnormalities has also been recently reported in children with CH (33.1%), especially in patients with ectopic thyroid gland (Ë).

The aim of this study is to find out the incidence of CH in the last year in the Italian Region of Piedmont, to assess the change in the etiology of CH and to analyze the rate of malformations and comorbidities in relation to the diagnostic category in a cohort of subjects referring to our tertiary regional Center.

METHODS

All newborns with diagnosis of primitive CH performed in a single tertiary center of Pediatric Endocrinology at Regina Margherita Children's Hospital of Turin were enrolled in the period

January 2014 - December 2018. Infants affected by syndromic CH or cromosomopathies, transient CH or isolated hyperthyrotropinemia in whom substitutive treatment has not been started, were excluded. Confirmation of the diagnosis of CH was based on serum levels of TSH, fT4, fT3 and thyroglobulin and on radiological evaluation with Tc99 scintigraphy, including ultrasound examination in case of suspected thyroid gland agenesis. Anti-peroxidase (AbTPO) and anti-thyroglobulin (AbHTG) antibodies have been evaluated in all newborns in case of unknown or positive maternal antibodies titre. To exclude neonatal jaundice, liver enzymes and bilirubin were evaluated in all subjects. All blood tests were performed in a single laboratory. A thorough clinical evaluation was performed in all newborns to assess malformations, comorbidities and symptoms related to congenital hypothyroidism. The malformations were identified based on clinical examination, echocardiography, X-ray of hand and lumbar spine, and ultrasonography of abdomen and pelvis. The clinical examination included the search for malformations or dysmorphisms, i.e. spinal defects, heart murmurs and CH-related symptoms. Replacement therapy was started as soon as possible with a liquid formulation of L-thyroxine at 10-15 mcg/kg/day administered once in the morning. On the basis of the etiology of CH, the cohort was divided into 4 subgroups, the one with thyroid gland agenesis, ectopia, hypoplasia and dyshormonogenesis .

Statistical analysis and graphs were performed by the Graphpad 7 software (GraphPad Software, La Jolla, CA, USA) using the chi-quadrate test to compare the rates among the different groups.

RESULTS

Eighty five newborns (48 males and 37 females) affected by CH were identified in the study period. The incidence of CH in the Italian region of Piedmont in the years 2014-2018 was 1:1000-1200. The demographic, biochemical and clinical data are represented in Table 1.

		Agenesis N=13	Ectopia N=21	Hypoplasia N=9	Dyshormonogenesis N=42	p
	Premature birth	2 (15.4%)	1 (4.7%)	3 (27.3%)	15 (35.7%)	***p*=0.04**
	M/F	6/7	8/9	7/4	27/15	*p*=0.49
	Vaginal delivery/ Caesarian delivery	6/7	12/7	5/6	19/23	*p*=0.61
	SGA	3 (23%)	4 (19%)	2 (18.1%)	10 (23.8%)	*p*=0.21
	Familiarity	3 (23.7%)	6 (28.5%)	3 (27.2 %)	13 (30.9 %)	*p*=0.94
Biochemical data	**TSH (µUI/ml)**	500.9±91.2	349.1±54	321.3±130.4	152.1±31.9	***p*<0.001**
	fT4 (pg/ml)	3.6±1.45	7.95±0.95	11.2±1.27	8.41±1.23	***p*<0.001**
	fT3 (pg/ml)	2.13±0.34	2.56±0.2	3.77±0.34	3.62±0.28	***p*<0.001**
	Thyroglobulin (ng/ml)	2.1±1.55	260.5±73.5	832.3±638.8	1578.9±406.9	***p*<0.001**
Clinical data	**Initial LT4 dose (µg/kg)**	11.3±0.54	9.7±0.3	8.7±0.94	9±0.4	***p*<0.001**
	Mean first year of life LT4 requirement (µg/kg)	6.4±0.19	6±0.18	5.8±0.44	5.5±0.42	*p*=0.22
	CH related symptoms	7 (53.8%)	7 (33.3%)	5 (55.5%)	15 (35.7%)	*p*=0.44
	Malformations	6 (46.1 %)	3 (14.2%)	2 (22.2%)	17 (40.5%)	*p*=0.11
	Comorbidities	1 (7.6 %)	0 (0%)	2 (22.2%)	4 (9.5%)	*p*=0.49
	Malformations and comorbidities	7 (53.8%)	3 (14.2%)	4 (44.4%)	21 (50%)	***p*=0.03**
	All	9 (69.2%)	8 (38 %)	8 (88.8%)	30 (71.4%)	***p*=0.02**

Thyroid scintigraphy revealed a dysgenesis of the gland in 50.6% (43/85) of the analyzed population. Thyroid agenesis was observed in 15.3% (13/85) of cases, while thyroid ectopia and hypoplasia respectively in 24.7% (21/85) and 10.6% (9/85) of all newborns with CH. Thyroid dyshormonogenesis with in situ gland was observed in 49.4% (42/85) of the cases. No difference was observed between the groups regarding sex, type of delivery, birth weight and length and familiarity for thyroid disease. Statistically significant higher prevalence of premature birth was

observed in case of dyshormonegenesis (15/42, 35.7%) and gland hypoplasia (3/9, 27.3%) compared to agenesis (2/13, 15.4%) or ectopia (1/21, 4.7%) **[*p=0.04*].**

As expected, serum TSH levels were higher in case of gland dysgenesis. TSH values were 500.9±91, 349.1±54 and 321.3±130.4 µUI/ml in case of thyroid agenesis, ectopia and hypoplasia respectively, while newborns with dyshormonogenesis displayed lower TSH levels (152.1±31.9 µUI/ml, ***p<0.001***). FT4 levels were higher in case of gland hypoplasia and dyshormonogenesis (11.2±1.27 pg/ml and 8.41±1.23 respectively) compared to the agenesis and ectopia (3.6±1.45 and 7.95±0.95 respectively) [***p<0.001***]. The same trend was recorded for fT3 levels (3.77 ± 0.34 and 3.62 ± 0.28 pg/ml compared to 2.13 ± 0.34 and 2.56 ± 0.2 pg/ml respectively, ***p<0.001***). Thyroglobulin levels were higher in neonates with dyshormonogenesis (1578.9±406.9 mg/dl) compared to all other groups (***p<0.001***). Newborns with thyroid agenesis, ectopia and hypoplasia displayed thyroglobulin levels of 2.1±1.55, 260.5±73.5, 832.3±638.8 mg/dl respectively.

The initial requirement for L-thyroxine was higher in the case agenesis and ectopia of the gland (11.3±0.54 and 9.7±0.3 µg/kg/d respectively, ***p<0.001***). In the case of thyroid hypoplasia, the initial dose was 8.7±0.94 µg/kg/d, whereas in neonates with thyroid dyshormonogenesis it was 9±0.4 µg/kg/d. No difference was observed in the mean daily requirement for the first year of life.

The symptoms related to CH are represented in Figure 1. The most frequent symptoms observed were jaundice and respiratory distress, while hypotonia, hypoglycemia or bradycardia were less present. No statistical difference was observed among the different groups.

Figure 1. CH-related symptoms at birth .

The malformations associated with CH are shown in Figure 2. Extra-thyroid congenital anomalies were observed in 30/85 (35.2%) of newborns with CH. The system most affected by the malformations is the cardiac system (15/85, 17.6%) followed by the urogenital tract (10/85, 11.7%),

the gastrointestinal tract (7/85, 8.2%), the musculoskeletal system (5/85, 5.9%), and the arteriovenous system (2/85, 2.4%).

Figure 2. Malformations associated with primary CH.

The highest rate of malformations was observed in the patients affected by thyroid agenesis and dyshormonogenesis, respectively 46.1% and 40.5%, while in the subjects with thyroid ectopia and hypoplasia the rate was 14.2% and 22.2% respectively, although the difference was not statistically significant.

The comorbidities observed for each group were epileptogenic encephalopathy in 1 subject with thyroid agenesia; stenosis of the lacrimal duct and severe atopic dermatitis in 2 subjects with glandular hypoplasia and anemia in 4 infants suffering from dyshormonogenesis. No comorbidities were observed among patients affected by thyroid ectopia.

Considering both malformations and comorbidities, subjects with ectopic thyroid gland showed a lower risk ***(p=0.03)***. The same trend is observed if CH-related symptoms are also considered ***(p=0.02).***

DISCUSSION

Primary CH is the most frequent congenital endocrine disorder that can lead to severe growth failure and delayed neuropsychomotor development when misdiagnosed and untreated. To avoid this, the neonatal screening strategy includes the measurement of TSH on dried blood spot (DBS) in the first days of life. In Italy this screening was firstly performed in 1984 and since then the cut-off level for referring to the Pediatric Endocrinology Departments has been continuously updated in all Italian Neonatal Screening Centers. The current cut-off level for TSH in the Piedmont Region are 8

μUI/ml at the first screening and 6.5 μUI/ml at the second one. This screening strategy has led to an increase in the prevalence of CH in the last 4 years from 1:3000-4000 to the actual 1:1000-1200. Another important factor influencing the increase in prevalence is the growing population of newborns at risk of CH such as preterm infants and babies born from multiple pregnancies. From the Regional Neonatal Screening Center, 0.8-1 % of all newborns (about 30.000 newborns/year) are re-called for a second screening of which 18-20% (40-50 newborns/year) is referred to the endocrinologist for further investigation on thyroid function. In 65-70% of cases a permanent CH is confirmed, while 30-35% have a transient hypothyroidism due to an immaturity of the hypothalamus-pituitary-thyroid axis, due to maternal factors or other causes that are still unknown, or it show a transient isolated mild hyperthyrotropinemia with normal fT4 levels that do not require substitutive treatment. The first effect of the increase in prevalence is the variation in the percentage of the different causes of CH; the current percentage of defects related to the gland in situ is 40-50% compared to 15-25% observed before the lowering of the TSH cut-off at screening and our data confirm this trend. This fact may be explained by the fact that this change in the neonatal screening strategy allows to diagnose mild forms of CH with thyroid gland in situ previously misdiagnosed. The remaining forms include thyroid dysgenesis: agenesis in about 15%, ectopia in 25% and hypoplasia in 10%.

Since the late 1980s, it is well known that CH is associated with a higher risk of other congenital abnormalities (10.5-59%), especially congenital heart diseases (CHD) that affect 8-14% up to 50% of all newborns with CH (U, AAA, BBB, CCC, DDD, EEE, FFF, GGG, QQQ, DH). Gu et al. (Ç) reported an extra-thyroid malformation rate of 14.6% in a Japanese series of 1520 subjects with CH, showing that the most frequent concomitance was with cardiovascular malformations (8.9%) followed by gastrointestinal and respiratory system (2.41%). Zahra et al reported congenital heart defects in 4.9% of infants with CH, while Bas et al (TT) detected malformations in 28.2% of all cases and the most common abnormalities were cardiovascular malformation (8.0%). (T) Reddy et al. (W) indicated extra-thyroid malformations in 10 (59%) of 17 patients, of which 29% of cardiac

defects and 41% of neural tube defects in the form of spina bifida occulta. Stoll et al. (ZZ) described extra-thyroid abnormalities in 15.5 % of cases with primary persistent CH and concluded that in this population congenital cardiac abnormality seems to be increased five-folds compared to the normal population (6.9%). In an Italian series affected by CH, the risk of congenital anomalies detected was higher (8.4%) than in the general population with cardiac defects in 5.5% of cases (LM). Conversely, in an Egyptian series, cardiovascular abnormalities were reported in 9.1%, the most frequent association represented by minor musculoskeletal anomalies, found in 47.7% of cases (FF) (FF). Kumar (DH) reported significant association with renal and urinary tract abnormalities. Kreisner et al. [QQ] detected malformations in 13.2% of 76 patients with permanent CH, mainly cardiac malformations, but also cleft palate and lip and bifid spine. Kempers at al showed higher morphological abnormalities in children with CH (33.1%), especially in patients with ectopic thyroid gland (Ë).

In our series, extra-thyroid congenital abnormalities were observed in 30/85 (35.2%) of infants with CH, a higher percentage than many other studies, especially if the previous Italian cohort that reported a malformation rate of 8.4% (LM) is considered. The most involved system is the cardiac system (15/85, 17.6%) followed by malformations of the urogenital tract (10/85, 11.7%), of the gastrointestinal tract (7/85, 8.2%), of the musculoskeletal system (5/85, 5.9%), and of the arteriovenous system (2/85, 2.4%).

In the present paper we also analyzed the rate of malformations for each subtype of CH, thyroid gland agenesis, hypoplasia or ectopia and the dyshormonogenesis. A higher rate was observed in the patients suffering from agenesis and dyshormonogenesis (46.1% and 40.5%, respectively) compared to subjects with hypoplasia or ectopia (22.2% and 14.2%, respectively), although this difference is not significant. No comorbidity was observed in the group affected by the ectopic thyroid gland; if both comorbidities and malformations are considered, the ectopic gland seems to to be less associated with other diseases. This might be explained by the fact that at the base of the thyroid agenesis and of the dyshormonogenesis different genes are involved which can lead to a

greater prevalence of alterations also in other organs in development compared to what happens for ectopia or thyroid hypoplasia

This represents the first study that analyzes the distribution of malformations and comorbidities associated with the different subtypes of CH, not only to CH as a whole. The main limit of this paper is the lack of genetic analyses, which could help to understand the mechanisms underlying CH and help in establishing a phenotype-genotype correlation. For that reason, the hypotheses raised here can be confirmed in further studies, which include an extensive genetic analysis on larger cohorts.

CONCLUSIONS

Primary CH is the most common inborn endocrine disorder, with an increasing prevalence due to new neonatal screening strategies and the increase of the newborns at risk for CH. The main effects of the increase in prevalence are the change in the percentage of the different forms of CH, with an increase of those with in situ gland, which currently seem to cover 40-50% of all causes of CH, and the increase in associated malformations, especially in the presence of agenesis of the gland or defects in the hormonogenesis.

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