Epidemiology of Congenital Hypothyroidism

6

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6.1 Introduction

Congenital hypothyroidism (CH) is defined as thyroid hormone deficiency present at birth. This condition is the most common congenital endocrine disorder and one of the most common preventable causes of mental retardation [1].

Institution of newborn screening for CH since 1970 and its development have provided the opportunity for early detection and treatment of CH and prevention of its neurodevelopmental consequences [2–5]. Furthermore, institution of regional and nationwide newborn screening programs for CH has provided essential epidemiological data which have been helpful in better understanding the natural history of the disease and in appropriate management of babies with CH [1, 6, 7].

In this chapter, the most important issues regarding epidemiology of CH will be reviewed and discussed.

6.2 Primary Congenital Hypothyroidism

Primary CH is the most common form of CH. It occurs as a result of developmental defects of the thyroid gland (dysgenesis) or is due to disruption in thyroid hormone biosynthesis (dyshormonogenesis). This leads to goitrous hypothyroidism, although it is rarely seen in babies detected by newborn screening [8].

About two thirds of the CH cases are due to thyroid dysgenesis, such as the arrested migration of the embryonic thyroid (ectopic thyroid), the lack of one – in most cases the left – lobe of the thyroid (hemiagenesis), or a complete absence of

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thyroid tissue (athyreosis). About one third of babies diagnosed as having hypothyroidism at recall examination had a normally located gland [9, 10]. Ten to fifteen percent are due to autosomal recessively inherited defects in hormone synthesis, whereas the remaining cases (15–20 %) are due to mild functional disorders [11–14].

Thyroid dysgenesis is generally thought to be sporadic, although the possibility of a genetic component is supported by some studies. One study of all cases of thyroid dysgenesis found that 2 % were familial [15]. Additional studies also showed that 7.9 % of first-degree relatives of infants with CH had a thyroid developmental anomaly [16].

Nearly all screening programs report a female preponderance among babies with thyroid dysgenesis, with a female-to-male ratio of about 2:1 [17, 18]. A report from Quebec shows that this female preponderance occurs mostly with thyroid ectopy and less with agenesis [19]. On the other hand, a female-to-male ratio of about 1:1 is generally reported among babies with normally located gland [18].

CH may also frequently be associated with an increased risk of congenital extrathyroidal malformations [20]. In our previous study conducted on 1,420 CH babies recorded in the Italian National Registry of Infants with Congenital Hypothyroidism (INRICH), extrathyroidal congenital malformations had a prevalence of 8.4 % [21]. Given the availability of a population-based registry, it was possible to study a high number of CH infants with extrathyroidal malformations and compare these data with those of the International Clearinghouse for Birth Defects, the worldwide database collecting information on infants born with congenital malformations. By using this approach, it was possible to demonstrate that not all congenital extrathyroidal malformations but only anomalies of heart, nervous system, eyes (representing precocious structures in the developing embryo), and multiple congenital malformations were significantly associated to CH. These findings have strongly suggested a very early impairment in the first stages of embryo development with a consequent involvement of different organs and structures [21]. Moreover, it was demonstrated that the most frequent cardiac malformations in the CH population were represented by the atrial septal defects, differently from that found in the general population in which the most frequent cardiac anomalies are represented by ventricular septal defects. Other associated malformations include spiky hair, cleft palate, neurological abnormalities, and genitourinary malformations [20, 22, 23].

6.3 Incidence of Primary CH

Prior to the onset of newborn screening programs, the incidence of CH, as diagnosed after clinical manifestations, was in the range of 1:7,000 to 1:10,000 [24]. With the introduction of newborn screening, the incidence was reported in the range of 1:3,000 to 1:4,000 [25]. It remained relatively constant until 1990 when a progressive rise in the rate was reported in the USA, Europe, and other parts of the world. Currently, the CH incidence rate is reported in the range of 1:1,660 to 1:2,828 live births (Table 6.1) [13, 26–30]. These rates refer to babies with confirmed CH

Table 6.1 Modifications of incidence rates of primary congenital hypothyroidism (confirmed at birth) reported worldwide

Country and period of observation	Incidence of CH	TSH cutoff (mU/L)	Re-sampling strategy for at risk categories of neonates	Country and period of observation	Incidence of CH	TSH cutoff (mU/L)	Re-sampling strategy for at risk categories of neonates	Reference
Western Australia 1981–87	**1: 5745**	>25	No	Western Australia 1988–98	**1: 2828**	>15	No	Kurninczuk (2002) [26]
New Zealand 1993–2001	**1: 3846**	>15	No	New Zealand 1993–2010	**1: 2778**	>15	No	Albert (2012) [27]
Quebec 1990–2000	**1: 2898**	>15[a] >15[b]	No	Quebec 2001–2009	**1: 2450**	>15[a] >5[b]	No	Deladoey (2011) [13]
Italy 1987–1998	**1: 3000**	>20	No	Italy 1999–2008	**1: 1940**	>10	Yes	Olivieri (2015) [30]
Greece 1990–99	**1: 3300**	>20	No	Greece 2000–2009	**1: 1749**	>10	Yes	Mengreli (2010) [29]
Massachussets (USA) 1991–1994	**1: 3000**	Cut-off T4: 7.2–10 µg/dl TSH with the lowest 10 % of T4	No	Massachussets (USA) 2003–2010	**1: 1660**	Cut-off T4: 13 µg/dl TSH with the lowest 10 % of T4	Yes	Mitchell (2011) [28]

[a]TSH cutoff on the 1st NBS test
[b]TSH cutoff on the 2nd NBS test

requiring the start of the replacement therapy. Some case–control studies have been conducted in different parts of the world to investigate the risk factors for CH [31–33]. In these studies, a common set of risk factors for the disease was identified which included birth defects, female gender, maternal diabetes, twins, preterm deliveries, and gestational age > 40 weeks.

6.4 Causes Influencing the Increasing Incidence of Primary CH

Several factors have been proposed to explain the cause of this approximate doubling of the incidence rate. These include changing in screening strategies and cut-offs, increase in preterm survival, demographic changes, and environmental factors. However, the higher incidence rate observed in the last decades worldwide includes additional cases of mild CH.

6.4.1 Seasonality

There was some speculation on a possible seasonal variation in the incidence of CH. However, this topic is still under debate. Studies demonstrating an increase in CH in the winter months have been conducted in Japan, Finland, Iran, and USA [33–36], indicating this is an effect that is observed globally in geographic areas with varying climates. In Japan, sex-specific seasonal patterns of incidence have been also found [37]. However, similar variations have not been confirmed in other parts of the world [27, 38–40].

6.4.2 Changes in Screening Strategies and Lowering TSH Cutoff

The increase of the CH incidence has been attributed to the widespread shift from primary T4 to primary TSH screening strategies and to the reduction of TSH cutoff [41, 42]. With increasing accuracy of TSH measurements on the small volume of blood available in the dried blood specimens obtained for screening, several programs employing a primary T4 test switched to a primary TSH test. Currently, most newborn screening programs around the world employ a primary TSH strategy, the exceptions being some state programs in the United States, Israel, the Netherlands, and some programs in Japan measuring free T4 and TSH simultaneously [43].

Data from the literature have shown that the impact of lowering TSH cutoff on the incidence of CH has resulted in a significant rise of the incidence with an increased detection of milder cases of CH [44]. As shown in Table 6.1 when the TSH cutoff was lowered from a range of >20–25 mU/L to >10 mU/L (whole blood), a doubling of the incidence of CH confirmed at birth was generally observed. An exception was represented by Quebec where the CH incidence increased less. It was 1:2,850 in the period 1990–2000 and 1:2,450 in the period 2001–2009. This lower

increase can be at least partially explained by the fact that the reduction of the TSH cutoff (from 15 to 5 mU/L) only concerned the second (recall) test, which is performed when the result of the first screening test (at 3–5 days of life with a cutoff of 15 mU/L) is positive [13].

An important clinical question is whether these milder cases of CH are transient or require permanent treatment. In our previous study conducted on the data of the INRICH, we have demonstrated that in the period 2000–2006 21.6 % of the Italian population of babies with permanent CH had a milder increase of TSH at screening (≤15.0 mU/L whole blood), whereas in the group of infants with transient hypothyroidism this percentage was 54 % [45]. In another Italian study conducted on a group of 84 Italian children with eutopic thyroid glands and mild CH, results of the reevaluation of the diagnosis after the age of 3 years showed that 35 % of these children had abnormal TSH elevations after thyroxine withdrawal and 27 % had persistent hyperthyrotropinemia (TSH 5–10 mU/L). A minority of cases had mutations in the genes commonly linked to mild forms of CH [46]. Taken together, these data suggest that newborns with mild abnormalities on neonatal screening have a significant risk of permanent CH that may become more severe in the future. Furthermore, babies with thyroid dysgenesis may have a mild increase of TSH at screening. In our more recent study conducted on 4,195 babies with a diagnosis of CH confirmed at birth and recruited in the INRICH, it was found that 8.7 % of infants with thyroid dysgenesis had a TSH at screening <15.0 mU/L whole blood. This finding can explain the slight increase (+8.0 %) of CH incidence due to thyroid dysgenesis observed in our analysis (from 1:4,000 live-borns in the period 1987–90 to 1:3,300 in the period 2007–08) [30]. Such a result was not found in other studies conducted in countries where screening programs adopted higher TSH cutoff or used T4 as the primary screening test [13, 28].

6.4.3 Premature Birth and Multiple Pregnancy

Thyroid dysfunction is frequently observed among comorbidities associated with prematurity. The most common pattern of thyroid dysfunction seen in preterm infants is transient hypothyroxinemia of prematurity (low T4 with normal TSH) which is observed in up to 50 % of infants born before 28 weeks [47]. In addition to transient hypothyroxinemia of prematurity, preterm babies have a higher incidence of primary CH, mostly with eutopic thyroid [48]. It has been reported that VLBW babies have a risk of CH about 14-fold higher than that of normal birth weight babies (1:250) [49]. Moreover, about two thirds of VLBW infants with CH detected on newborn screening show a delayed TSH rise [49, 50]. The timing of this elevation generally occurs between 2 and 4 weeks of age. According to recent guidelines [6, 7], NBS programs in the USA and Europe now collect a second specimen at 2–4 weeks of life in special categories of at-risk neonates, including babies born preterm [28–30, 51, 52].

Preterm babies show a high risk of both permanent and transient CH. In the Italian population of infants with CH recorded in the INRICH between 1987 and

2008, the frequency of preterm babies was 12.4 % among infants with permanent CH and 30.7 % among babies with transient hypothyroidism ascertained by reevaluation of the diagnosis. These frequencies were significantly higher than the 6.5 % observed in the Italian newborn population in the same period [30]. Improvements in perinatal and neonatal care have increased the survival rate of a growing number of preterm babies [53]. Therefore, with improved survival rates more preterm and LBW infants, who would previously have died in the newborn period, now have a greater potential to be tested and confirmed to have CH. This fact has been confirmed by a recent analysis conducted on data of the INRICH demonstrating that about 50 % of the increased incidence of CH observed in Italy between 1987 and 2008 (from 1:3,000 to 1:1,940 live-borns) was attributable to preterm babies, including those with low TSH at birth who have been identified by means of a low TSH cutoff and special procedures for at-risk newborns (resampling at 2–4 weeks of life) [30]. Another factor which can affect the frequency of preterm babies with CH is the iodine nutritional status. Because the ability to escape from the Wolff-Chaikoff effect does not mature until 36 weeks, preterm babies are at risk of hypothyroidism from excess iodine exposure due to topical application of iodine antiseptics [41]. However, as preterm infants have lower iodine stores and greater iodine requirements than term infants, they are also at risk of thyroid hypofunction due to iodine deficiency. This risk is particularly high in hospitalized preterm infants. In fact, it has been demonstrated that a hypothetical 1 kg preterm infant would receive less than the recommended 30 μg/kg/day with any standard nutritional regimen (enteral and parenteral nutrition) [54].

As regards twins, recent decades have seen a major increase in multiple birth rates globally, given the increasing use of techniques of assisted reproduction and drugs inducing ovulation [55, 56]. In our previous study conducted on the INRICH data, a risk of CH occurrence was found threefold higher in twins than in single deliveries. The estimated CH incidence was 10.1 per 10,000 live births in multiple deliveries and 3.2 per 10,000 live births in single deliveries [57]. Moreover, the analysis of reevaluated infants with high suspicion of transient hypothyroidism recorded in the INRICH has also shown a twin prevalence of 1.9 % among infants who resulted affected by permanent CH and 13.2 % in those with final diagnosis of transient CH. Taken together, these findings have demonstrated an increased risk for both permanent and transient CH in multiple than in single pregnancies.

6.4.4 Demographic Changes

Changes in the ethnic composition of the population have been also reported as a potential cause of the worldwide rise in CH incidence, as different ethnic groups may have a different risk for CH. In the USA, white newborns have been reported to have a higher risk of CH than black infants. Moreover, between 1991 and 2000, the highest incidence rate of CH in the USA was found in Hispanic newborns, and this rate was associated with a high percentage of Hispanic births in that period [58]. In another study conducted in New Zealand, it was found that the rate of dyshormonogenesis in

hypothyroid cases was associated with higher birth rates among Asian and Pacific populations [27]. Beside the ethnicity and the fertility rate of a population, the prevalence of consanguinity among parents is an important factor that can help to explain certain differences in CH incidence rates. In our recent study conducted on the data of the INRICH between 1999 and 2008, consanguinity was found to be significantly higher among African (24 %), Asian (13 %), and Hispanic CH babies (9.0 %) than Caucasian CH babies (Italian 2.0 % and East-European 1.6 %). Moreover, in the same period, the group of babies born to consanguineous parents showed a significantly higher frequency of normal/hyperplastic thyroid than of thyroid dysgenesis (65 % vs 35 %, $P<0.05$), suggesting a high occurrence of genetically determined dyshormonogenesis among babies born to consanguineous parents [30].

6.5 Transient Forms of CH

Transient hypothyroidism may be caused by maternal or neonatal factors. Maternal factors include antithyroid medications [59], transplacental thyrotropin receptor blocking antibodies, which are relatively rare causing transient congenital hypothyroidism in approximately1:100,000 neonates [60], and exposure to iodine deficiency or excess. Neonatal factors include neonatal iodine deficiency or excess [5], congenital liver hemangiomas [61], and mutations in the genes encoding for DUOX and DUOXA2 [62, 63]. In an Italian case–control study, preterm delivery was described as being an independent risk factor for transient CH [31]. In another study conducted in Greece, a higher prevalence of transient hypothyroidsm was shown in premature compared with full-term infants [29]. However, the most common causes of transient CH still remain iodine deficiency or overload, particularly in premature newborns. According to iodine intake in the population, transient CH is found to be more common in Europe (1:100) than in the USA (1:50,000) [1]. In Italy, over a period of observation of 10 years (1999–2008), 58 % of CH cases reevaluated after a withdrawal of the replacement therapy at 2–3 years of age showed transient hypothyroidism [30].

6.6 Secondary (Central) Congenital Hypothyroidism

While most CH cases are due to CH of thyroidal origin (primary CH) manifesting as thyroid dysgenesis or thyroid hormone synthesis defects, a significant number of CH cases are due to inadequate thyroid-stimulating hormone (TSH) secretion from the anterior pituitary [64–66]. This category of CH cases is termed as CH of central origin (secondary CH). Congenital TSH deficiency may rarely be an isolated problem (caused by mutations in the TSH beta subunit gene), but most commonly it is associated with other pituitary hormone deficiencies, as part of congenital hypopituitarism [1].

Newborn screening programs for secondary CH are active only in few countries worldwide. Moreover, the incidence of this condition has been reported with a rate

ranging widely between 1:106,304 and 1:16,404 [67–69]. This variability can be essentially explained by different screening strategies and methods used in different countries. The Northwest Regional Newborn Screening Program in the USA, using a primary T4 test approach with a cutoff <10th percentile, reported a central CH incidence of 1:106,304 [67]. The Kanegawa prefecture of Japan, measuring free T4 in the dried blood spot with follow-up of infants with a free T4 < 0.7 ng/dl, reported an incidence of 1:30,833 [68]. The newborn screening program in the Netherlands, using a primary T4 test with TBG and TSH measured in samples from infants with a T4 < 5th percentile, detected central CH with an incidence of 1:16,404 [69].

Conclusion

Over the years, availability of epidemiological data from population-based and local surveillance systems have contributed to increase understanding on the incidence, cause, treatment, and outcome of CH. On the other hand, new data have raised new questions. Therefore, new epidemiological studies are needed to further improve knowledge on CH, to promote and orient future molecular studies to more precise targets, and to support clinical research.

Moreover, a recent epidemiological evaluation of the current status of screening programs for CH around the world estimated that approximately 71 % of babies worldwide are not born in an area with an established newborn screening program [43]. This implies that despite the existence of newborn screening for over five decades in developed countries, the majority of babies with CH worldwide are not detected and treated early. New efforts should be done to establish new screening programs for CH and to avoid that the economic burden of neuropsychological sequelae of the disease remains a significant public health problem in many countries.

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