Incidence of Congenital Hypothyroidism Over 37 Years in Ireland

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BACKGROUND AND OBJECTIVES: Congenital hypothyroidism (CHT) is one of the most common preventable causes of learning disability. Newborn screening with whole-blood thyroid-stimulating hormone measurements was introduced in the Republic of Ireland in 1979 and is coordinated from a single center with an unchanged protocol since its inception. Our objective in this study was to describe the incidence of CHT in the Republic of Ireland over the past 37 years in the context of a complete national population and an unchanged screening protocol.

METHODS: The newborn screening records of all individuals who were diagnosed with CHT between 1979 and 2016 were reviewed. Infants with positive screening results had a whole-blood thyroid-stimulating hormone value of ≥15 mU/L at 72 to 120 hours of life; values of 8 to 15 mU/L required a repeat whole-blood screening test.

RESULTS: Of 2,361,174 infants who were screened between July 1979 and December 2016, 1063 (662 girls) were diagnosed with CHT (incidence: 0.45 cases per 1000 live births). The number of detected cases increased from 0.27 cases per 1000 live births treated between 1979 and 1991 to 0.41 cases per 1000 live births treated between 1992 and 2004 to 0.65 cases per 1000 live births treated between 2005 and 2016. The increase in detected cases of CHT was predominantly in the normal or hyperplastic gland category.

CONCLUSIONS: The incidence of CHT has increased significantly in the Republic of Ireland over the past 37 years despite a consistent screening cutoff. The increased rate was not explained by an increased survival rate of preterm infants or a changing population heterogeneity.

WHAT’S KNOWN ON THIS SUBJECT: The incidence of congenital hypothyroidism is increasing worldwide. Changes in thyroid-stimulating hormone screening cutoffs over time are considered to be one of the main contributing factors.

WHAT THIS STUDY ADDS: The incidence of congenital hypothyroidism has increased significantly in Ireland over a 37-year period, represented by an increase in cases with a normal gland. The increased incidence is not explained by a change in thyroid-stimulating hormone screening cutoffs over time.
Congenital hypothyroidism (CHT) is the most commonly detected endocrine abnormality on newborn screening and has a reported incidence of ~1 in 2000 to 4000 births.1-4 Newborn screening programs have been in place over the last 40 years in most industrialized countries and have led to the successful early detection and treatment of infants with CHT and have almost eliminated the severe neurodevelopmental deficits that result from a late diagnosis.5

Most cases of CHT are primary, isolated, and permanent either because of an abnormal thyroid gland development (thyroid dysgenesis) or abnormalities of thyroid hormone biosynthesis in a structurally normal gland (thyroid dyshormonogenesis).6,7 Less commonly, an abnormal neonatal thyroid function is transient and is due to the transplacental passage of maternal blocking antibodies, iodine deficiency or excess, or immaturity of the hypothalamic-pituitary-thyroid axis.6 CHT may also rarely result from pituitary or hypothalamic abnormalities (termed central hypothyroidism), which are estimated to occur in 1 in 20 000 births.8 Thyroid imaging in which 99mTc or 123I and ultrasound are used has a role in differentiating these etiologies of CHT.9 Recent reports suggest that the incidence of CHT is increasing. In New York, the incidence increased by 138% over 27 years (from 0.29 cases per 1000 births in 1978 to 0.7 cases per 1000 births in 2005).1

Similar increases have been observed in Western Australia (from 0.17 cases per 1000 births between 1981 and 1987 to 0.35 cases per 1000 births between 1998 and 1999) and Italy (from 0.33 cases per 1000 births between 1987 and 1998)2 and Italy (from 0.33 cases per 1000 births between 1987 and 1998 to 0.51 cases per 1000 births between 1999 and 2008).10 Potential explanations for this observation include changes in population ethnic composition,3 environmental changes (such as perchlorate exposure),11 iodine deficiency,12 and changes in clinical practice13 and awareness that lead to better detection. Many screening programs’ cutoff levels have changed over time, which may partially explain the increased case ascertainment rate.10,14-16

Newborn screening for CHT in the Republic of Ireland began in July 1979 with a centralized newborn screening program for the entire country. Unlike other screening programs, the same assay and a consistent screening whole-blood thyroid-stimulating hormone (TSH) cutoff level of 8 mU/L has been used in the newborn screening program since the program’s inception in 1979. The unchanged Irish screening program cutoff (maintained over 37 years) provides an excellent opportunity to study the incidence of CHT over this time. Our aim in this study was to describe the incidence of CHT over the past 37 years in the context of a complete national population and an unchanged screening protocol.

METHODS

The Ethics Committee of Temple Street Children’s University Hospital approved this study. The population-based prospective records of the Republic of Ireland’s National Newborn Bloodspot Screening Program for CHT, coordinated from the Temple Street Children’s University Hospital (1979–2016), were reviewed.

In the Republic of Ireland, whole-blood samples are collected on filter paper after a heel prick from all infants between 72 and 120 hours after birth. Whole-blood TSH concentration is measured by AutoDELFIA Immunoassay (PerkinElmer, Inc, Waltham, MA), and this assay has been used throughout the study period. Since 1979, 3 international reference materials (calibrants) have been used to calibrate the PerkinElmer assay. Before being circulated, each new calibrant has been evaluated against the previous calibrant to ensure continuity of measurement (stability). If the whole-blood TSH concentration is >15 mU/L, serum TSH and free thyroxine (FT4) are requested, and the patient is referred for evaluation to a pediatric endocrinologist. If the whole-blood TSH level is between 8 and 15 mU/L, a second newborn screen sample is requested within a recommended time frame of 7 days. If this repeat measurement is >8 mU/L, serum TSH and FT4 concentrations are measured, and the patient is referred for assessment. The infant’s and mother’s thyroid peroxidase antibody concentrations and the mother’s thyroid function are also measured to identify cases of CHT secondary to maternal antibodies. A special screening procedure is in place for preterm infants in the Republic of Ireland; this includes a measurement of whole-blood TSH levels at 72 to 120 hours with repeat screening weekly until term corrected gestational age.

Currently, thyroid scintigraphy is performed on all infants who have positive screen results and are able to attend the National Screening Centre at Temple Street Children’s University Hospital and Our Lady’s Children’s Hospital, Crumlin in Dublin or at Cork University Hospital. When infants are unable to attend for the scintigraphy or when a thyroid scintigraphy reveals no uptake, a thyroid ultrasound is performed. CHT is classified as thyroid dysgenesis (athyreosis, ectopy, and hypoplasia) or normal/hyperplastic gland on the basis of imaging. Follow-up care is provided either by a pediatric endocrinologist or a local pediatrician according to local availability and family preference. The aim in our screening program was to commence thyroxine (T4)
replacement by day 14 of life until 2005. Since 2005, the aim was to begin T4 replacement by day 10 of life. The recommended levothyroxine dose was 10 to 15 μg/kg daily, and infants with low pretreatment FT4 concentrations were treated with the highest initial dose.

**Patient Population**

All infants who were diagnosed with CHT and treated with levothyroxine in the Republic of Ireland between 1979 and 2016 were identified. Age at screening, TSH concentration on newborn screen results, thyroid function test results at diagnosis, sex, gestational age, ethnicity, comorbidities, thyroid imaging results (if performed), presence of medical iodine exposure, and family history of thyroid disease were recorded for all patients from 1979 to 2016. The screened cohort was subdivided into 3 groups according to year of birth (period 1 [1979–1991], period 2 [1992–2004], and period 3 [2005–2016]) to identify changes in incidence over time. Incidence of CHT was calculated by using the yearly birth rate provided by the Central Statistics Office (www.cso.ie). CHT severity was categorized on the basis of serum FT4 levels as mild (10–15 pmol/L), moderate (5–9.9 pmol/L), and severe (<5 pmol/L).9

To identify whether the increase in CHT incidence over this long study period in our screening program represented a true increase or a change in practice over time (with a tendency to treat milder cases), we compared the incidence of CHT in patients treated with serum TSH concentrations of 8 to 20, 21 to 40, 41 to 100, and >100 mU/L, separately.

**Detailed Follow-up (Period 3 Group)**

All patients who were diagnosed with CHT in period 3 (2005–2016) were reevaluated at age ≥3 years to describe the incidence of transient and permanent CHT. The primary physician (local pediatrician or pediatric endocrinologist who was looking after the patient) was contacted to establish if the patient was receiving ongoing treatment with levothyroxine, establish the current dose, their most recent weight, and details of any known comorbidities. Patients who had dysgenesis on imaging or increasing levothyroxine dose requirements in childhood were classified as having permanent CHT. For patients with a confirmed normal or hyperplastic gland on initial imaging, their primary physician was contacted to clarify if they had ever undergone a trial-off treatment. Patients with no interval increase in T4 dose who had not previously had a trial-off treatment were reevaluated. This reevaluation comprised stopping levothyroxine treatment and checking serum TSH and FT4 concentrations at 2, 6, and 12 weeks from stopping treatment. If thyroid function tests remained within the reference range, the patient was classified as having transient CHT. If the serum TSH concentration rose to >10 mU/L after complete withdrawal of treatment, permanent CHT was diagnosed, and levothyroxine was restarted. If the serum TSH concentration rose slightly (5.5–10 mU/L), patients were managed, and if the mild hyperthyroptropinaemia persisted, they were evaluated with a thyrotropin-releasing hormone test to confirm primary hypothyroidism; if primary hypothyroidism was confirmed, levothyroxine was restarted.

**Statistical Analysis**

All statistical analyses were performed by using SPSS 22.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY). Because of the nonnormal distribution of data, statistical analyses are presented as medians and interquartile ranges (25th and 75th percentile). The Mann–Whitney U test was used to compare groups of nonnormally distributed data, and an independent sample t test was used for normally distributed data. An analysis of variance was used for group comparisons. A P value of <.005 was considered statistically significant.

**RESULTS**

**Overall Incidence of CHT**

Of 2,361,174 infants who were screened for CHT in the Republic of Ireland between July 1979 and December 2016, 1,063 (662 girls) were diagnosed with CHT (incidence 0.45 cases per 1000 births; Fig 1). Of these, 102 infants (9.6%) were born preterm. Diagnostic imaging (radioisotope uptake scan and/or thyroid ultrasound) was performed in 903 cases (85%), of which 482 (53.4%) cases had thyroid dysgenesis (270 ectopy, 174 athyreosis, and 38 hypoplasia; Table 1). The number of detected cases of CHT increased over the study period from 224 cases treated in period 1 (1979–1991; incidence: 0.27 cases per 1000 births) to 288 cases treated in period 2 (1992–2004; incidence: 0.41 cases per 1000 births) to 551 cases treated in period 3 (2005–2016; incidence: 0.65 per cases 1000 births). Imaging was not consistently performed in the earliest time period of the study (period 1). In periods 2 and 3, the increase in detected cases of CHT was predominantly in the normal or hyperplastic gland category (accounted for 23% of cases in period 2 but 47% of cases in period 3), whereas the incidence of thyroid dysgenesis remained stable over the study period (Fig 2).

**Incidence of CHT According to Severity**

Over the study period, the incidence of treated CHT increased in infants with initial serum TSH concentrations of 8 to 20 mU/L; however, the largest increase was seen in infants with initial serum TSH concentrations of
21 to 40 mU/L and 41 to 100 mU/L. CHT incidence remained relatively constant in infants with initial serum TSH concentrations of >100 mU/L (Fig 3). We compared the incidence of mild, moderate, and severe CHT over the study period and showed that the increased incidence was seen in the mild CHT cohort (Fig 4).

All patients who were treated in period 3 (2005–2016) were assessed to determine if they had transient or permanent CHT (n = 551). The incidence of transient and permanent CHT in children >3 years of age throughout period 3 is presented in Fig 5. Complete data were available on 524 (95%) patients. There were 210 patients who had confirmed thyroid dysgenesis (ectopy: n = 107; agenesis: n = 79; hypoplasia: n = 24) and, therefore, permanent CHT. Of the remaining 314 patients, 229 were eligible (normal or hyperplastic gland and aged >3 years at the time of the study) for reevaluation. Of these, 49 patients were excluded because CHT was secondary to maternal antibodies (n = 4), iodine exposure (n = 17), and trisomy 21 (n = 28).

To look at predictors for transient and permanent CHT, we excluded patients who were exposed to iodine and patients with hypothyroidism secondary to maternal antibodies because these are already known to be transient causes of hypothyroidism. Patients with trisomy 21 were not traditionally given a trial-off treatment, and therefore, we excluded infants with a diagnosis of trisomy 21. Of the 180 patients with a normal or hyperplastic gland, 86 (47.7%) had transient CHT, and 94 (52.2%) had permanent CHT.

A comparison of these children who had transient and permanent CHT with a normal or hyperplastic gland showed that the increased incidence was seen in the mild CHT cohort (Fig 4).
The incidence of athyreosis and ectopic glands has remained relatively constant in the 3 different time windows (1979–1991, 1992–2004, and 2005–2016). However, the incidence of infants with normal thyroid glands on imaging has increased in each period.

FIGURE 2
The incidence of athyreosis and ectopic glands has remained relatively constant in the 3 different time windows (1979–1991, 1992–2004, and 2005–2016). However, the incidence of infants with normal thyroid glands on imaging has increased in each period.
FIGURE 3
The annual incidence of CHT with initial serum TSH concentrations between 1979 and 2016 in the Republic of Ireland. A, Initial TSH concentration of 8 to 20 mU/L. B, Initial TSH concentration of 21 to 40 mU/L. C, Initial TSH concentration of 41 to 100 mU/L. D, Initial TSH concentration of >100 mU/L.
reported an increasing incidence of CHT, which most likely reflects changes in TSH cutoffs. This has been shown in Italy (where the TSH cutoff was changed from 15 to 7 mU/L, resulting in a 26% increase in permanent CHT and a 57% increase in transient CHT10), France,24 Quebec,24 Greece,17 and Serbia.25 Longitudinal studies in the United States (1978–2005)1 and New Zealand (1993–2010)26 have revealed an increase in incidence; however, between 1989 and 2000 in the United States, the number of births of Asian American infants increased by 37%, and the number of births of Hispanic infants increased by 53%. Asian American infants have a higher incidence of CHT, with authors of some studies reporting the incidence to be 3 times higher in Asian American infants than the average in infants in Europe.27 Changes in demographics accounted for 45% to 50% of the increase in the incidence of CHT in New York.1 Although there had been no change in screening cutoffs over time, the authors also reported that methodologies and instrumentation had changed over the study period.1 In a study of the incidence of CHT in New Zealand, the authors reported an interval increasing incidence with no change in screening cutoffs. Changes in the ethnicity of the population was postulated to be responsible for the observed increased incidence, similar to the study from New York in which a significant increase in the rate of births of Asian American infants during the study period was seen.26 Unlike these studies, our patient population has not experienced significant changes in ethnicity over the study period, and the reference standard that is used in Ireland has remained unchanged.

The availability of thyroid imaging results in this study allowed us to demonstrate that the increased incidence of CHT over the study period was in cases of CHT with
a normal or hyperplastic gland. A larger proportion of infants did not have imaging performed in period 1, making it difficult to compare the incidence of cases with a normal gland between periods 1 and 2; however, cases with a normal or hyperplastic gland were responsible for 23% of all cases of CHT that were diagnosed in period 2, compared with 47.2% of all cases of CHT that were diagnosed in period 3. This pattern was also seen in an Italian study in which the proportion of infants with CHT who had a normal gland increased from 18% between 1987 and 1998 to 42% between 1999 and 2000.

Changing population ethnicity may also contribute to changes in CHT rates. The highest incidence rate of CHT in the United States between 1991 and 2000 was found in Hispanic newborns. The study population was predominantly white, and the incidence of CHT in people of color was too low to show an effect on the CHT incidence. With special screening procedures for preterm infants and improved survival rates, more preterm infant survivors who might have previously died in the newborn period may be screened for CHT. In our study, preterm infants accounted for 3.9% of cases in period 2 and 15.4% of cases in period 3; however, the incidence of CHT almost doubled between periods 2 and 3 compared with a recent Italian study in which preterm infants accounted for 58% of the increased incidence. Therefore, the increased incidence of CHT in Ireland cannot be fully explained by increased survival rates of preterm infants.

Although changes in screening cutoffs and treatment practices over time are considered to be the main contributing factors to the previously described increasing incidence of CHT worldwide, other potential causes for the reported increase have been suggested. These include changes in population ethnic composition, environmental changes, such as perchlorate exposure, and iodine deficiency. Unlike other European countries, Ireland does not have a salt iodization program and may consequently have a relatively high prevalence of iodine insufficiency. In 2006, a study of Irish pregnant women suggested a prevalence of iodine deficiency in 55% of women who were tested in summer and in 23% of women who were tested in winter, and a more recent Irish study supported a link between fetal thyroid function and maternal iodine intake.

Changing population ethnicity may also contribute to changes in CHT rates. The highest incidence rate of CHT in the United States between 1991 and 2000 was found in Hispanic newborns. Our study population was predominantly white, and the incidence of CHT in people of color was too low to show an effect on the CHT incidence. With special screening procedures for preterm infants and improved survival rates, more preterm infant survivors who might have previously died in the newborn period may be screened for CHT. In our study, preterm infants accounted for 3.9% of cases in period 2 and 15.4% of cases in period 3; however, the incidence of CHT almost doubled between periods 2 and 3 compared with a recent Italian study in which preterm infants accounted for 58% of the increased incidence. Therefore, the increased incidence of CHT in Ireland cannot be fully explained by increased survival rates of preterm infants.

The main strength of this study is the comprehensive availability of clinical data and thyroid imaging in infants with CHT who were born over a 37-year period in a relatively homogenous white population with an unchanged newborn screening procedure and assay. This allows for us to describe changing patterns of CHT over time. However, the main weakness is that it is not possible to demonstrate that there has been a change in the number of cases of untreated transient CHT with mildly elevated TSH concentrations. Although all such infants with mildly elevated serum TSH levels were managed until the TSH levels had normalized, the data on infants with untreated, mildly elevated TSH levels was not captured in periods 1 and 2 by the National Newborn Bloodspot

### Table 2: Comparison of Children With a Normal Thyroid Gland on Imaging Who Had Transient or Permanent CHT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total, N = 180</th>
<th>Transient, n = 86</th>
<th>Permanent, n = 94</th>
<th>P ( ^{a} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male-to-female sex ratio</td>
<td>1.1:1.16</td>
<td>1.1:1.35</td>
<td>1:1.02</td>
<td>.55</td>
</tr>
<tr>
<td>Birth wt, kg, median (IQR)</td>
<td>3.3 (2.7–3.7)</td>
<td>3.2 (2.5–3.7)</td>
<td>3.3 (2.9–3.7)</td>
<td>.50</td>
</tr>
<tr>
<td>Gestational age, wk, median (IQR)</td>
<td>39 (38–40)</td>
<td>39 (38–40)</td>
<td>40 (38–40)</td>
<td>.52</td>
</tr>
<tr>
<td>Age at treatment initiation, d, median (IQR)</td>
<td>11 (9–17)</td>
<td>13 (10–17.7)</td>
<td>10 (8–15)</td>
<td>.25</td>
</tr>
<tr>
<td>Whole-blood TSH levels, mU/L, median (IQR)</td>
<td>17 (11–35)</td>
<td>14 (10–21)</td>
<td>21 (13–71.5)</td>
<td>.000</td>
</tr>
<tr>
<td>Serum TSH levels at diagnosis, mU/L, median (IQR)</td>
<td>50.6 (28.6–77)</td>
<td>38.6 (25.1–66.4)</td>
<td>67.2 (54.3–101.2)</td>
<td>.002</td>
</tr>
<tr>
<td>Serum FT4 levels at diagnosis, pmol/L, median (IQR)</td>
<td>11.9 (8.4–16.2)</td>
<td>12.8 (9.6–16.9)</td>
<td>11.4 (9.0–15.2)</td>
<td>.008</td>
</tr>
<tr>
<td>Initial levothyroxine dose, µg/kg per d, median (IQR)</td>
<td>10.1 (7.3–13.1)</td>
<td>9.6 (6.9–12.3)</td>
<td>11.2 (7.5–14)</td>
<td>.03</td>
</tr>
</tbody>
</table>

IQR: interquartile range

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1. Mann–Whitney U test was used to compare transient CHT with permanent CHT.
Screening Program because only data on infants who were treated were prospectively collected in the earlier periods. These data are now collected prospectively and will be explored in future studies.

CONCLUSIONS
We have shown that the incidence of CHT has increased significantly in the Republic of Ireland over a 37-year period (represented by an increase in mild but significant cases of CHT with a normal or hyperplastic gland). The increased incidence is not explained by a change in the TSH screening cutoff, screening procedure over time, or population ethnic composition. Increased survival rates of preterm infants contributed to but did not explain the increase in CHT case detection. Other potential causes, such as iodine deficiency or excess and environmental factors, need to be considered.

ACKNOWLEDGMENTS
We thank the vision of Dr Seamus Calahane, who was instrumental in setting up the Irish screening program for CHT, Dr Sylvia Dockery, Mr Richard Walsh (principal biochemist), Prof Michael Cullen, Prof Veronica Donoghue (consultant radiologist), and Prof Thomas Clarke, who managed the initial care of these infants for many years with Dr Colm Costigan, Dr John McKiernan, and Prof Hilary Hoey, the commitment of the many midwives and public health nurses who undertook sample collection and follow-up, the staff of the National Newborn Bloodspot Screening laboratory, the staff of the Day Ward, the radiographers and radiologists at Temple Street Children’s University Hospital, and the many pediatricians and pediatric endocrinologists in the Republic of Ireland who provided and continue to provide care to these infants and have supported this study.

ABBREVIATIONS
CHT: congenital hypothyroidism
FT4: free thyroxine
T4: thyroxine
TSH: thyroid-stimulating hormone

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POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Dr McGrath is supported by a grant from The Children’s Fund for Health at Temple Street Children’s University Hospital. The other authors received no external funding.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2018-2262.

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Pediatrics 2018;142;
DOI: 10.1542/peds.2018-1199 originally published online September 21, 2018;

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