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Original article

Increased incidence of congenital hypothyroidism in France from 1982 to 2012: a nationwide multicenter analysis

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ABSTRACT

Purpose: Recent studies have shown an increased incidence of congenital hypothyroidism over the past 2 or 3 decades. The etiology of this change is unknown, but it has been related by several authors to lowering of cutoffs. We sought to determine whether the incidence of congenital hypothyroidism (CH) in France has changed.
Methods: We analyzed data from the nationwide neonatal screening program for CH during the period 1982–2012. We included all children having thyroid-stimulating hormone values above the threshold and for whom diagnosis of CH confirmed by the pediatrician. We estimated multicentric temporal trends in the annual incidence rates adjusted for screening methods for thyroid dysgenesis and eutopic gland.
Results: We found 6622 cases of CH (28.0 per 100,000 newborns); 1895 had a eutopic gland, and 4727 had thyroid dysgenesis. The incidence of eutopic glands showed a significant annual average increase of (5.1%; 95% confidence interval: 4.3–5.9) regardless of the screening method or screening center. This increase was confirmed in severe cases (thyroid-stimulating hormone ≥50: 2.1%; 95% confidence interval, 1.4–2.9). The incidence of dysgenesis remained constant.
Conclusions: The incidence of eutopic glands increased in France, not only in mild forms but also in severe cases.

Introduction

Congenital hypothyroidism (CH) is a condition of thyroid hormone deficiency present at birth. Untreated hypothyroidism results in severe mental impairment. Newborn screening programs in the first days of life are useful for implementing early treatment via a thyroid hormone, thereby avoiding abnormal neurodevelopment. Congenital primary hypothyroidism (CH) is estimated to occur in approximately one in 3000–4000 live births in iodine-sufficient regions throughout the world [1], mainly due to thyroid dysgenesis. This term refers to an abnormality in embryological development of the thyroid gland because of defects in thyroid differentiation (athyreosis) and thyroid migration (ectopy). The remaining cases can be attributed to inborn errors in thyroid hormone synthesis, also called dyshormonogenesis (eutopic glands). Most cases of CH occur sporadically. However, dyshormonogenesis cases are often recessively inherited [2], and recent cohort analyses

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estimate that approximately 2% of cases of thyroid dysgenesis are familial [3]. CH is classified into permanent and transient forms. Permanent CH refers to persistent thyroid hormone deficiency requiring life-long treatment. Transient CH refers to temporary thyroid hormone deficiency, discovered at birth, which eventually reverts to normal thyroid hormone production.

An increased global incidence of CH has been reported in the United States [4,5], Quebec [6], New Zealand [7], Italy [8], Argentina [9], and Greece [10] over the past 2–3 decades. In some studies, changes in the ethnic composition of the screened population were considered to be the cause of the increase [7,11]. Although inherent screening limitations do exist, most of this increase has been ascribed to lowering of cutoffs [6,8–10,12]. The increase in reported diagnoses, therefore, could reflect more benign or transient cases of identified CH [12,13]. Recently, a study carried out on US data, with adjustment for laboratory methods, concluded that there existed an increase in the global incidence [14]. However, because of uncertainties, an increase in CH incidence over time remains subject to debate.

In France, the nationwide newborn screening program for CH was implemented in the 1980s. The aim of the present study was to describe incidence changes in CH from 1982 to 2012 in France. We estimated multicenter temporal trends of annual incidence rates adjusted for screening methods for both thyroid dysgenesis and eutopic glands.

Materials and methods

French CH neonatal screening program

The neonatal screening program for CH began in France in 1978 and was progressively generalized throughout the country, covering all newborns since 1980. This program is under the responsibility of the French Association for Screening and Prevention of Child Handicaps (AFDPHE, Association Française pour le Dépistage et la Prévention des Handicaps de l'Enfant) and is supported by the National Health Insurance System (CNAMTS, Caisse Nationale d'Assurance Maladie des Travailleurs Salariés). In France, the CH screening program is multicentric and is managed by regional associations cooperating with regional laboratories. CH screening is based on whole-blood thyroid-stimulating hormone (TSH) measurement as a primary marker, on dried blood samples collected on filter paper (FP) from all newborns after 3 days of life. Depending on the center, TSH was measured either by immunofluorimetric (DELFIA; Perkin Elmer, Turku, Finland) or immunoradiometric assay (RIA; Iba-CisBio, Gif-sur-Yvettes, France). From 1982–2001, the cutoffs for the two methods varied between 20 and 30 mU/L and were set by each laboratory following their own TSH percentiles. For this first period, we decided to fix the TSH threshold at 30 mU/L. Since 2002, availability of the first TSH-certified reference material produced by the Centers for Disease Control and, thereafter, production of reference material by the International Society for Neonatal Screening led to defining national TSH cutoffs at 20 mU/L for DELFIA and 25 mU/L for immunoradiometric assay methods [15].

Infants with TSH below the threshold were considered as free of CH. When values were above the threshold, the child was considered at risk for CH, and a second measurement on blood from the initial Guthrie card was performed in duplicate. If the second TSH measurement stayed greater than the threshold, the newborn was referred to a pediatrician competent in CH management. A diagnostic workup was then performed, with additional clinical, biological, and morphological tests to confirm the diagnosis. To clarify the etiology of CH, thyroid ultrasound scan and/or scintigraphy were performed to determine the presence, location, type, and size of the thyroid tissue. A replacement therapy with L-thyroxine was initiated for all confirmed CH. All cases were registered via a standardized questionnaire filled in by the pediatrician and centralized in the AFDPHE anonymous database. In the present study, children were considered as having CH if they had TSH values above the threshold and if the diagnosis of CH was confirmed by the pediatrician after diagnostic workup. Results reported here were derived from this AFDPHE database. For reasons related to the quality of data, this study is based on data collected since 1982. This study received approval from The French Commission on Individual Freedom and Data Storage ("Commission Nationale de l'Informatique et des Libertés", CNIL, approval no. 1614365).

Statistical analyses

We analyzed temporal trends in annual incidence rates of newborns with CH between 1982 and 2012. The yearly incidence was expressed as the number of CH cases per 100,000 births and was calculated using the number of diagnosed cases divided by the number of screened newborns. Long-term trends in CH with eutopic glands and thyroid dysgenesis were handled separately.

Because the response variable comprised yearly aggregated counts, we considered it appropriate to model the numbers of diagnosed cases with a Poisson distribution. For each CH type, the annual numbers of diagnosed cases were analyzed according to the number of screened newborns and regressed with time, adjusting for the screening method factor. The logarithm of numbers of screened newborns according to center, screening method, and year was then included in the model as an offset term. A cubic regression spline was used for investigating the general shape of long-term temporal trends. To assess the impact of screening method on trends, we added an interaction between the method and time in the model. To take into account the hierarchical

Table 1
Number of CH cases by diagnosed group and overall incidence rates per year, metropolitan France, 1982–2012

Year	Dysgenesis	Eutopic gland	All CH	Newborns tested	Incidence rate of CH per 100,000 births
1982	157	20	177	792,801	22.4
1983	131	31	162	744,445	21.8
1984	155	26	181	755,403	24
1985	148	24	172	767,927	22.4
1986	149	27	176	778,504	22.7
1987	152	35	187	768,293	24.4
1988	135	32	167	768,139	21.8
1989	141	47	188	758,46	24.8
1990	159	37	196	760,907	25.8
1991	160	47	207	756,998	27.4
1992	133	50	183	742,735	24.7
1993	142	45	187	709,062	26.4
1994	155	58	213	708,312	30.1
1995	161	47	208	723,685	28.8
1996	145	55	200	738,748	27.1
1997	127	49	176	726,768	24.3
1998	149	58	207	745,577	27.8
1999	158	57	215	744,383	28.9
2000	176	62	238	777,857	30.6
2001	187	67	254	776,621	32.8
2002	155	58	213	768,597	27.8
2003	168	77	245	763,212	32.2
2004	159	88	247	768,525	32.2
2005	165	95	260	772,499	33.7
2006	160	70	230	792,928	29.1
2007	144	106	250	785,403	31.9
2008	165	75	240	797,98	30.1
2009	155	84	239	791,507	30.2
2010	149	122	271	800,008	33.9
2011	151	119	270	793,973	34.1
2012	136	127	263	789,341	33.4
Total	4727	1895	6622	23,669,598	28