Variation by Ethnicity in the Prevalence of Congenital Hypothyroidism Due to Thyroid Dysgenesis

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Background: The scant data on ethnic differences in the prevalence of congenital hypothyroidism (CH) have generally not taken etiology of CH into account. Our hypothesis is that the prevalence of CH due to thyroid dysgenesis (TD) varies by ethnicity.

Methods: This case-control study included all patients with CH due to TD (a condition of unknown origin) or to dyshormonogenesis (DH, of known autosomal recessive transmission) between 1987 and 2009. Etiology was established by ^{99m}Tc scintigraphy. The parents self-assessed their ethnicity, which we grouped in Caucasian, Hispanic, black, Asian, and Maghreb/Middle East. We compared ethnicity between the 190 patients with TD (147 ectopies, 40 athyreoses, and 3 orthotopic hypoplasias) and the 44 patients with DH. Ethnicity was also compared to the reference population of the city of Montreal. Prevalence odds ratios (POR) were calculated and compared by the bilateral Fisher's exact test.

Results: The ethnic composition of the DH group was similar to that of the reference population. In blacks, TD prevalence of 1 in 190 (0.5%) was low compared to that of DH (4 in 44; 9.1%; POR 0.06; 95% confidence interval: 0.001–0.56; $p = 0.005$). In contrast, Caucasians showed an increased TD prevalence of 166 in 190 (87.3%) compared to that of DH (30 in 44; 68.2%; POR 3.21; 95% confidence interval: 1.37–7.34; $p = 0.0052$). No statistically significant differences were observed between other ethnic groups.

Conclusion: TD is less prevalent in blacks and more prevalent in Caucasians. Blacks being more genetically diverse, this is an argument for an oligogenic inheritance of susceptibility to TD.

Introduction

CONGENITAL HYPOTHYROIDISM (CH) is the most common congenital endocrine disorder with a prevalence of 1 case in 3000 live births (1). In about 85% of cases, it results from thyroid dysgenesis (TD), a condition comprising defects in the differentiation, migration, or growth of thyroid tissue (2). The etiological diagnosis of CH is established through thyroid scintigraphy (3). Incomplete migration resulting in ectopic thyroid tissue [(sub)lingual thyroid] is the most common form of dysgenesis (up to 80%). On one hand, oligogenic inheritance of susceptibility with low penetrance is suggested by (i) the fact that 2% of cases TD have an affected relative, which is 15-fold higher than what would be expected by chance alone (4) and by (ii) a model based on molecular studies of different mice strains heterozygous for *Pax8* and *Ttf1* genetic ablation (5). On the other hand, a survey of monozygotic twins, which yielded a discordance rate of 92% (6), and the documented sexual dimorphism in TD (7) suggest that non-Mendelian mechanisms likely account for the majority of cases of TD. To unify these apparently divergent models, we proposed a two-

hit model that would be compatible with the usual sporadicity seen in TD and the evidence for a complex genetic contribution in some familial cases (8). In this model, a combination of two genetic hits (first hit: either *de novo* germinal hit or inherited susceptibility polymorphisms; second hit: germinal or somatic mutation in a different locus) in threshold-sensitive genes involved in thyroid development could lead to TD.

Ethnic variations in prevalence may reflect differences in genetic susceptibility caused by polymorphisms or differences in environmental exposures (e.g., environmental contaminants). However, environmental causes operating *in utero* are unlikely because (i) no temporal or seasonal trends for TD have been observed (1), and (ii) monozygotic twins who are discordant for TD have similar birth weights (G. Van Vliet, unpublished observations). In this context, if genetic susceptibility plays a role, the prevalence by ethnicity of TD should vary. Unfortunately, the scant data on ethnic differences in the prevalence of CH have not taken etiology of CH into account (9–12), or if etiology was available, only two ethnic groups (i.e., Asian and non-Asian) were eventually compared (13) (Table 1).

TABLE 1. LITERATURE ABOUT INCIDENCE OF CONGENITAL HYPOTHYROIDISM BY ETHNICITY

References	Year	Area covered	Ethnicity	Incidence ^a /percentage ^b
Brown <i>et al.</i> (10)	1979–1981	Georgia	White	1:5526
			Black	1:32,377
			Oriental	1:2128
Grant and Smith (27)	1982–1984	England, Wales, Northern Ireland	Black	0.6% ^b
Rosenthal <i>et al.</i> (13)	1981–1987	North West of England	Asian	12% ^b
			Asian	1:918
Lorey and Cunningham (11)	1982–1989	California	Non-Asian	1:3391
			Asian	1:4464
			Black	1:10,989
			Hispanic	1:1785
			Native American	1:2493
			White	1:4166
			Other	1:3906
Roberts <i>et al.</i> (28)	1979–1992	Atlanta	Non-Hispanic White	1:4400
			Black	1:10,000
Kaiserman <i>et al.</i> (9)	1979–1987	Israel	Asia	1:4425 ^c
			Africa	1:4464 ^c
			America/Europe	1:3367 ^c
			Israel	1:7476 ^c
			White	1:3533
Waller <i>et al.</i> (12)	1990–1998	California	Hispanic	1:2217
			Black	1:11,494
			Black/Hispanic	1:4149
			Asian ^d	1:2506

^aIncidence of CH (all etiologies included).

^bPercentage of ethnic group is given, as no information on ethnic composition of the reference population is available.

^cWe used maternal ethnicity as in our study.

^dWe used the same ethnic group as our study. Asian included Filipino, Chinese, Vietnamese, Japanese, Korean, and Asian Indian. CH, congenital hypothyroidism.

Therefore, to assess whether the prevalence of TD varies by ethnicity, we conducted a retrospective case-control study to compare ethnic groups in patients found to have TD by scintigraphy to that of patients found to have dysmorphogenesis (DH, of known autosomal recessive transmission), this latter group being similar in ethnicity to the reference population.

Patients and Methods

We retrospectively reviewed all charts of patients in whom CH due to TD was diagnosed at the Sainte-Justine Hospital (i.e., ectopic thyroid and athyreosis) or to DH between 1987 and 2009. The screening procedure in Québec has been previously described (7,14). The diagnoses were confirmed by serum thyrotropin (TSH) and free thyroxine (fT₄) and the etiology was established by ^{99m}Tc scintigraphy. The diagnosis of athyreosis was made when scintigraphy showed no perchlorate uptake together with an undetectable level of thyroglobulin (Tg), to avoid overdiagnosis (i.e., TSH receptor or sodium/iodide symporter (NIS) mutation causing apparent athyreosis). However, in three patients from the DH group with a family history of DH and a palpable goiter at diagnosis a thyroid scan was not performed. The parents were asked to self-assess their ethnicity, which was validated by the treating physicians. In keeping with the ethnic group definition of Statistics Canada, the different groups were Caucasian, Hispanics, Asians (including South Asian, Southeast Asian, Chinese, and Filipino), Maghreb/Middle East (including Lebanon),

and blacks (including Afro-American, Haitian, and African). The patients ($n = 7$) whose maternal and paternal ethnicities were different had been assigned to the maternal ethnic group. We then compared ethnicity in the 190 patients with TD (147 ectopies, 40 athyreoses, and 3 orthotopic hypoplasias) with that of the 44 patients with DH. Ethnicity was also compared to the reference population of the city of Montreal, averaging the 2001 and 2006 census (data from Statistics Canada; www.statcan.gc.ca); accurate data on ethnicity were not freely available for previous census. Other collected data included gender of the patient; method of delivery; gestational age; presence of other birth defect; chronological and bone age at diagnosis; biochemical data, including plasma TSH, fT₄, triiodothyronine, and Tg at diagnosis; and paternal and maternal age.

Statistical analysis was performed using statistical software R (15). The prevalence in the different ethnic groups was compared by the bilateral Fisher's exact test and the calculated odds ratio of prevalence was reported as prevalence odds ratio (POR). To correct for multiple comparisons (i.e., Bonferroni correction), p -values < 0.008 (for comparison between DH group and the reference population; six groups compared; power of 99.6%) and < 0.01 (for comparison between DH and TD groups; five groups compared; power of 98.7%) were considered statistically significant. The expected number of patients was calculated with chi-square goodness of fit test by classifying observed numbers of the reference population, DH patients and TD patients by two variables (i.e., ethnic group and rest of the population).

TABLE 2. COMPARISON BETWEEN OUR CONTROL GROUP (DYSHORMONOGENESIS) AND THE REFERENCE POPULATION OF THE CITY OF MONTREAL

Origin	DH (%)	Population (%) of the city of Montreal census 2001	Population (%) of the city of Montreal census 2006	Population (%), average of census 2001 and 2006	Odds ratio (95% CI)	p-Value ^a
Caucasian	30 (68.2)	787,975 (77.2)	1,178,895 (74)	983,435 (76.1)	0.68 (0.35–1.37)	0.22
Hispanic	2 (4.5)	31,190 (3.1)	53,965 (3.4)	42,578 (3.3)	1.33 (0.16–5.11)	0.66
Asian ^b	4 (9.1)	96,905 (9.5)	147,185 (9.2)	122,045 (9.5)	0.96 (0.25–2.65)	1.0
Maghreb/Middle East	4 (9.1)	29,755 (2.9)	N/A	N/A	N/A	N/A
Black African	4 (9.1)	68,245 (6.7)	122,880 (7.7)	95,562 (7.4)	1.25 (0.32–3.46)	0.57
Other (non specified ethnicity)	0 (0)	5665 (0.6)	90,800 (5.7)	48,232 (3.7)	N/A	N/A
Total	44 (100)	1,019,735 (100)	1,593,725 (100)	1,291,852 (100)		

^ap-Value <0.008 was considered statistically significant (bilateral Fisher's exact test) to correct for comparing five ethnic groups and one group of nonspecified ethnicity (i.e., Bonferroni correction).

^bAccording to Statistics Canada, Asian include people from South Asian, Southeast Asian, Chinese, and Filipino; South Asian include people from India, Pakistan, and Sri Lanka; Southeast Asian include people from Vietnam, Cambodia, Malaysia, Laos, and nearby areas.

95% CI, confidence interval of 95%; DH, dyshormonogenesis; N/A, not available.

Other results were expressed as mean and standard deviation for normally distributed data and as median and range for non-normally distributed data.

Results

Ethnic composition of the group with CH due to DH

To determine if the DH group is an appropriate control group, we compared its ethnic composition to that of the reference population of the city of Montreal (Table 2). No statistically significant differences were observed between DH and the reference population. Therefore, the DH group was used as control.

Variation by ethnicity in prevalence of CH due to TD

To assess whether ethnic composition in TD differs from control subjects, we compared the prevalence of ethnic groups in TD and DH (Table 3). In blacks, TD prevalence of 1 in 190 (0.5%) is low compared to that of DH (4 in 44; 9.1%; POR 0.06; 95% confidence interval: 0.001–0.56; $p = 0.005$). Consistent with this, the number of cases of TD in blacks (only one) is lower than the expected number of 14. In contrast, Caucasians show an increased TD prevalence of 166 in 190 (87.3%) compared to that of DH (30 in 44; 68.2%; POR 3.21; 95% confidence

interval: 1.37–7.34; $p = 0.0052$), the observed number of 166 Caucasians in TD being higher than the expected number of 145. No statistically significant differences were observed for other ethnic groups.

Other data analysis: perinatal characteristics of patients and information relating to the diagnosis of CH

The other data we collected essentially confirm what we and others have previously reported (16) (Table 4): proportions of etiological groups, female predominance in TD but not in DH, presence of cardiovascular defects in 5.8% of TD patients, and greater severity of CH in TD—likely due to the athyreoses—than in DH (TD vs. DH: median TSH 238.4 vs. 44 mU/L, $p = 0.0003$; median fT₄ 6.2 vs. 9.1 pmol/L, $p = 0.033$; median triiodothyronine: 1.7 vs. 2.7 nmol/L, $p = 0.0001$; median Tg: 80.5 vs. 464 µg/L, $p = 0.0001$; absence of ossification center of the knee 21.7% vs. 4.8%, $p = 0.014$). More DH than TD patients were born by caesarean section (25.6% vs. 8.9%, $p = 0.007$). Mean gestational age was 39.5 weeks in TD and 39.1 weeks in DH ($p = 0.042$); however, by dividing gestational age into 3 periods (<37, 37–40, and >40 weeks), we did not find any difference between TD and DH. Paternal and maternal age did not differ between TD and DH.

TABLE 3. COMPARISON BETWEEN THE CONTROL GROUP (DYSHORMONOGENESIS) AND THYROID DYSGENESIS PATIENTS REGARDING ETHNICITY

Origin	DH, n (%)	Expected number ^a of patients with DH	TD, n (%)	Expected number ^a of patients with TD	Odds ratio (95% CI)	p-Value ^b
Caucasian	30 (68.2)	33	166 (87.3)	145	3.21 (1.37–7.34)	0.0052*
Hispanic	2 (4.5)	1	7 (3.7)	6	0.80 (0.15–8.21)	0.68
Asian	4 (9.1)	4	6 (3.2)	18	0.33 (0.07–1.66)	0.1
Maghreb/Middle East	4 (9.1)	3	10 (5.3)	7	0.56 (0.15–2.56)	0.31
Black African	4 (9.1)	3	1 (0.5)	14	0.06 (0.001–0.56)	0.005*
Total	44 (100)	44	190 (100)	190		

^aThe expected number of patients was calculated with chi-square goodness of fit test by classifying observed numbers of the reference population, DH patients and TD patients by two variables (i.e., ethnic group and rest of the population).

^bp-Value <0.01 (bilateral Fisher's exact test) was considered statistically significant (*) to correct for comparing five ethnic groups (i.e., Bonferroni correction).

TD, thyroid dysgenesis.

TABLE 4. PERINATAL CHARACTERISTICS OF THE PATIENTS AND INFORMATION RELATING TO THE DIAGNOSIS OF CONGENITAL HYPOTHYROIDISM

Characteristics	TD	DH	Odds ratio (95% CI)	p-Value ^a
Children (n)	190	44		
	Ectopies: 147 (77.4%)			
	Female/male: 113/34 (3:1)			
	Athyreoses: 40 (21.0%)			
	Female/male: 28/12 (2:1)			
	3 hypoplasias (1.6%)			
Female/male	142/48 (3:1)	19/25 (~1:1)	4.03 (1.94–8.49)	<0.0001*
Father's age (mean ± SD) (years)	31.7 ± 6.6	32.2 ± 5.4		0.65
Mother's age (mean ± SD) (years)	29.4 ± 5.5	29.6 ± 5.1		0.87
Reported consanguinity (n)	2	1	0.46 (0.02–27.61)	0.46
Delivery method ^b				
Spontaneous, n (%)	124 (68.5)	23 (53.5)	1.71 (0.83–3.50)	0.12
Induced labor, n (%)	33 (18.2)	8 (18.6)	0.95 (0.39–2.57)	1
Caesarean, n (%) ^c	16 (8.9)	11 (25.6)	0.28 (0.11–0.72)	0.007*
Induced and cesarean, n (%)	8 (4.4)	1 (2.3)	1.86 (0.24–85.77)	1
Gestational age, mean (±SD)	39.5 (1.9)	39.1 (1.6)		0.042*
<37 weeks, n (%)	15 (7.9)	6 (13.6)	0.54 (0.18–1.83)	0.24
37–40 weeks, n (%)	112 (58.9)	28 (63.7)	0.82 (0.39–1.69)	0.61
≥41 weeks, n (%)	63 (33.2)	10 (22.7)	1.68 (0.75–4.07)	0.21
Twin pregnancy	3	2	0.34 (0.04–4.18)	0.24
Birth defect				
CHD, n (%)	11 (5.8)	0	Inf (0.59–inf)	0.23
Skeletal, n (%)	0	1 (2.3)	0 (0–9.03)	0.19
Neurological, n (%)	1 (0.5)	1 (2.3)	0.24 (0.003–19.29)	0.35
Urogenital, n (%)	1 (0.5)	0	Inf (0.005–inf)	1.0
Unremarkable, n (%)	177 (93.2)	42 (95.4)	0.65 (0.07–3.04)	0.74
Bone age at diagnosis ^d				
Normal, n (%)	87 (48.3)	31 (73.8)	0.35 (0.16–0.75)	0.004*
Slightly delayed, n (%)	54 (30)	9 (21.4)	1.54 (0.67–3.40)	0.35
Delayed, n (%)	39 (21.7)	2 (4.8)	5.40 (1.30–48.00)	0.014*
Lab finding at diagnosis				
TSH (mU/L), median (range)	238.4 (6.6–1473)	44 (3.6–837.9)		0.0003*
fT ₄ (pmol/L), (median–range)	6.2 (0.1–39.8)	9.1 (2.7–17.7)		0.033*
T ₃ (nmol/L), median (range)	1.7 (0.2–3.7)	2.7 (1–4.2)		0.0001*
Tg (μg/L), median (range)	80.5 (0.1–781.4)	464 (0.1–8154.4)		0.0001*
Start of LT ₄ (days), median (range)	13 (6–96)	12 (1–1610)		0.29
LT ₄ dosage [μg/(kg day)], median (range)	11.9 (3.4–17.5)	11.1 (3.1–15.9)		0.09

^ap-Value <0.05 was considered statistically significant (*); bilateral Fisher's exact test for proportion and Student's *t*-test for normal variables.

^bInformation not available for nine patients with TD and one patient with DH.

^cThe rate of caesarean delivery in Canada (1993) is 18%, and the rate of induced labor in Quebec is 18.7% (1995) (www.phac-aspc.gc.ca/rhs-ssg/phic-ispc/pdf/indperif.pdf).

^dInformation not available for 10 patients with TD and 2 patients with DH.

CHD, congenital heart defect; fT₄, free thyroxine; Inf, *ad infinitum*; LT₄, levothyroxine; SD, standard deviation; T₃, triiodothyronine; Tg, thyroglobulin; TSH, thyrotropin.

The median age at diagnosis and thus at introduction of levo T₄ treatment was similar in both groups (13 vs. 12 days, *p* = 0.29) as was the median dose of levo T₄ [11.9 vs. 11.1 μg/(kg day), *p* = 0.09]. These data show that in most cases of CH referred to our clinic, the treatment is initiated promptly with an appropriate dosage.

Discussion

The genetic basis of TD is still elusive (17,18). Oligogenic inheritance of susceptibility with low penetrance has been suggested as molecular mechanism (4,5), whereas non-Mendelian mechanisms are also involved considering the usual sporadicity and the high discordance rate for TD be-

tween monozygotic twins (6,8). A two-hit model combining inherited susceptibility polymorphisms with germ line or somatic mutation at a second locus in threshold-sensitive genes involved in thyroid development is therefore plausible for TD and has recently been shown to be relevant for a severe form of mental retardation (19). Our present findings showing variation by ethnicity in the prevalence of TD supports the hypothesis that susceptibility polymorphisms contribute to the disease. The genetic diversity in blacks (20) may protect them against diseases such as TD. In contrast, Caucasians are prone to develop TD, which is in keeping with (i) a decreased genetic diversity in Caucasians (i.e., bottleneck effect) and, consequently, with (ii) greater deleterious genetic variation in Caucasians than in blacks (21).

Indeed, we show here a decreased prevalence of TD among blacks. Interestingly, congenital heart septation defects (i.e., ventricular and atrial septal defects) are more prevalent in TD patients than in the general population (22,23), and they are also seen less frequently among blacks (24). Moreover, thyroid cancers are also less prevalent among blacks (25). The high degree of genetic diversity of blacks, especially in gene ontology groups involved in regulation of morphogenesis (GO No. 0022603) (20), might protect them against TD and perhaps thyroid cancer. This link between development and cancer also makes biological sense. For example and consistent with this idea, *NKX2.1* (i.e., a gene involved in thyroid development and listed in the GO No. 0022603) is also involved in thyroid cancer (26).

Altogether, TD is less prevalent in blacks and more prevalent in Caucasians. Lower prevalence of CH in blacks has been previously reported, but without grouping according to etiology (9–12). Lorey and Cunningham (11) showed no female predominance for CH in the black ethnic group (Table 1), which can be accounted for by the rarity of TD in blacks. Therefore and to our knowledge, the present study is the first that clearly establishes that blacks show a lower prevalence of the dysgenetic form of CH (TD), whereas their prevalence of functional CH (DH) is comparable to that of the reference population. Blacks being more genetically diverse (20), this variation of prevalence by ethnicity is an argument for an oligogenic inheritance of susceptibility to TD.

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Disclosure Statement

The authors declare that no competing financial interests exist.

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