Brief Report

Association between Thyroxine Levels at Birth and Choanal Atresia or Stenosis among Infants in Texas, 2004–2007

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BACKGROUND: The causes of choanal atresia or stenosis (CA) are largely unknown. Infant thyroxine (T_4) levels collected during newborn screening may be proxy measures for a risk factor present during the critical period of development. Therefore, we conducted a case-control study to examine the association between newborn T_4 levels and CA. **METHODS**: Data for cases with CA and controls were obtained from the Texas Birth Defects Registry for the period of 2004 to 2007. Information on infant T_4 levels at birth was obtained from the Texas Newborn Screening Program. Controls ($n = 3570$) were drawn from unaffected births in Texas for the same period and frequency matched to cases ($n = 69$) on year of birth, then linked to the newborn screening database. Logistic regression was used to evaluate the association between continuous and categorical infant T_4 levels and nonsyndromic CA. **RESULTS**: After adjustment for gestational age and year of birth, infant T_4 levels were inversely associated with CA (adjusted odds ratio [AOR], 0.85; 95% confidence interval [CI], 0.80–0.90). We observed a linear trend ($p < 0.001$) across quartiles of T_4; compared to infants with low levels, AORs for CA were 0.50 (95% CI, 0.28–0.91), 0.39 (95% CI, 0.20–0.75), and 0.15 (95% CI, 0.06–0.40) for infants with medium-to-low, medium, and high levels, respectively. **CONCLUSIONS**: Our findings suggest a role of low thyroid hormone levels in the development of CA, or that low newborn T_4 levels are potential proxy measures of a risk factor present during the critical period. *Birth Defects Research (Part A) 94:951–954, 2012.* © 2012 Wiley Periodicals, Inc.

Key words: choanal atresia or stenosis; thyroxine; newborn screening; birth defects

INTRODUCTION

Choanal atresia or stenosis (CA) is the most common craniofacial defect of the nose, occurring in approximately 1 in every 8000 to 10,000 births (Barbero et al., 2008; Burrow et al., 2009). CA is characterized by a narrowing or complete blockage of the openings between the nasal cavity and the pharynx (i.e., choanae) owing to bony or membranous growths in one or both openings (Corrales and Koltai, 2009). CA can be life threatening for

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newborns, and infants with CA often require multiple corrective surgeries and are at a higher risk of having respiratory distress (Friedman et al., 2000; Daniel, 2006). Despite its clinical significance, the etiology of CA is largely unknown (Case and Mitchell, 2011). Some studies have suggested that the use of certain antithyroid medication (i.e., methimazole and its prodrug carbimazole) during pregnancy may increase the risk of having a child with CA, although it is unknown to what extent the association is attributable to the medication, maternal thyroid disease, or abnormal levels of thyroid hormones (Di Gianantonio et al., 2001; Barbero et al., 2008; Kannan et al., 2008; Clementi et al., 2010).

Abnormally high or low levels of thyroid hormones early in life are associated with serious medical conditions (e.g., congenital hypothyroidism), which can lead to developmental delay and mental retardation (Krude et al., 1997; LaFranchi, 2011). Because of this, thyroid hormone levels are routinely measured as part of newborn screening efforts. As CA develops early in pregnancy (i.e., 6–11 weeks' gestation), infant thyroid activity at birth may not be reflective of the levels of thyroid hormones during the critical period of development. However, it is possible that infant thyroxine (T_4) levels collected as part of newborn screening may be proxy measures for a risk factor present during the critical period. There are currently no studies that have examined the association between the levels of thyroid hormones in newborns with CA. Therefore, the objective of this study was to examine the association between T_4 levels at birth and CA using data from the Texas Birth Defects Registry (TBDR) and the Texas Newborn Screening (NBS) Program. Given that the newborn T_4 levels are potential proxy measures of the thyroid hormone levels during the critical period, our hypothesis was that variability within the normal range of T_4 levels among newborns is associated with CA.

MATERIALS AND METHODS

Data on infants with CA delivered between July 2004 and December 2007 were obtained from the TBDR. The TBDR is a population-based, active surveillance system that has monitored births, fetal deaths, and terminations throughout the state since 1999. CA cases had a ''definite'' diagnosis (British Pediatric Association, code 748.0) during their first year of life. Any live-born infant with CA classified as having a definite diagnosis required documentation of the postnatal diagnosis in the medical records. All cases were then classified as syndromic or nonsyndromic (i.e., not associated with a chromosome abnormality or recognized malformation syndrome or sequence). For our analysis, we included only nonsyndromic cases. Controls were unaffected births (i.e., births not included in the TBDR) drawn from Texas birth certificates for the same study period (July 2004 to December 2007) and frequency matched to cases with CA on year of birth at a ratio of 5:1 (controls to cases).

Information on infant T_4 levels, collected from each infant 1 to 2 days after delivery, was obtained from the Texas NBS Program. Texas routinely performs at least two newborn screening tests on each infant (the first is 1 to 2 days after delivery and the second is 7 to 14 days after delivery). Only the initial NBS T_4 test was used for this analysis. Because infants with medical conditions detected by newborn screening would have abnormal T_4 levels, they were excluded from our study. Ultimately, only one control (diagnosis: congenital adrenal hypoplasia) and no cases, based on NBS, were excluded. Furthermore, infants who received blood transfusions were also excluded.

Information on maternal demographic and infant characteristics was collected from vital records and included infant sex (male or female); maternal age at delivery (<20, 20–24, 25–29, 30–34, ≥35 years); maternal race or ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other); parity (0, 1, ≥2); maternal education (<12, 12, >12 years); birth weight (grams); and gestational age (weeks).

Frequency distributions of maternal demographics and characteristics for case and control infants were calculated. Comparisons were made using chi-square tests for categorical variables (i.e., infant sex, maternal age, race or ethnicity, parity, and education) and *t* tests for continuous variables (i.e., birth weight, gestational age). To examine the association between infant thyroxine (T_4) levels and nonsyndromic CA, unconditional logistic regression was used to calculate crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Infant T_4 levels were assessed as a continuous exposure and were also classified by using quartiles (based on the distribution among controls) defined as: <14.58 μg/dL (reference), 14.58 to 17.44 μg/dL, 17.45 to 20.59 μg/dL, and ≥20.60 μg/dL. In the quartile analysis, the lowest quartile was selected as the reference category given the small of cases in the highest quartile. In addition, tests for trend were conducted using quartiles of T_4.

The following variables were incorporated as confounders in the final model if their inclusion resulted in ≥10% change in the estimate of effect between continuous T_4 levels and CA: infant sex, maternal age at delivery, race or ethnicity, parity, education, birth weight, and residence on the border (i.e., Texas-Mexico) at delivery. In addition, year of birth was included in the final models because it was a matching factor, and gestational age was included to account for potential differences in T_4 levels by gestational age. Finally, information on self-reported maternal thyroid disease and thyroid medication use during pregnancy was abstracted from medical records and used for sensitivity analyses. All analyses were conducted using Intercooled Stata, version 12.1 (StataCorp LP, College Station, TX).

RESULTS

During the period of 2004 to 2007, 93 CA cases were identified in Texas, and 69 were nonsyndromic. A total of 3570 singleton controls were frequency matched on year of birth to CA cases at a ratio of 5:1 and linked to the NBS database. In general, there were no differences between case and control mothers on selected demographic characteristics (Table 1). However, the mean birth weight was higher among control infants (3283 gm) compared with case infants (3115 gm; $p = 0.02$).

Overall, there was a significant crude negative association between continuous infant T_4 levels and CA, which remained after adjusting for gestational age and year of birth (Table 2). Neither birth weight nor any of the other variables that were evaluated appeared to confound the relationship between infant T_4 levels and CA. When infant T_4 was assessed as a continuous variable, there was a 15% decrease in the odds of CA with each 1μg/dL

Table 1
Maternal Demographic Characteristics among Choanal Atresia or Stenosis Cases and Controls: Texas, 2004–2007

	Cases (n = 69)[a]		Controls (n = 3570)	
	n	%	n	%
Infant sex				
Male	31	44.9	1735	48.6
Female	38	55.1	1835	51.4
Maternal age at delivery (years)				
≤20	10	14.5	455	12.8
20–24	16	23.2	1025	28.7
25–29	21	30.4	994	27.8
30–34	15	21.7	719	20.1
≥35	7	10.1	377	10.5
Race or ethnicity				
Non-Hispanic white	19	27.5	1246	34.9
Non-Hispanic black	11	15.9	397	11.1
Hispanic	37	53.6	1764	49.5
Other	2	2.9	160	4.5
Parity				
0	23	33.3	1378	38.6
1	22	31.9	1112	31.2
≥2	24	34.8	1053	29.5
Education (years)				
<12	24	35.3	1070	30.1
12	18	26.5	949	26.7
>12	26	38.2	1541	43.3
Birth weight (gm; mean [SD])[b]	3114.87 (558.85)		3283.45 (518.68)	
Gestational age (weeks; mean [SD])	38.13 (2.29)		38.49(1.79)	

[a]Nonsyndromic cases of choanal atresia or stenosis.
[b]*t* test: $p = 0.02$.

increase in T_4 levels, after adjusting for gestational age and year of birth (adjusted OR [AOR], 0.85; 95% CI, 0.80–0.90). In addition, CA cases had lower mean infant T_4 levels compared with controls (Supplemental Fig. 1).

In the analysis using the categorical T_4 variable, the crude negative association between infant T_4 levels and CA was significant in all categories when compared with the lowest category (<14.58 μg/dL). These associations remained significant after adjusting for gestational age and year of birth. Specifically, compared to infants with low T_4 levels, the AORs for CA were 0.50 (95% CI, 0.28–0.91), 0.39 (95% CI, 0.20–0.75), and 0.15 (95% CI, 0.06–0.40) for infants in the medium-low, medium, and high levels, respectively. This trend was statistically significant ($p < 0.001$). In addition, one case mother reported hyperthyroidism and one case mother reported use of thyroid medication (i.e., Synthroid) during pregnancy. We repeated the analyses excluding these individuals, and our results did not change (data not shown).

DISCUSSION

In one of the first studies of its kind, we found a significant association between low infant T_4 levels and CA. Although little is known about the etiology of CA, this finding contributes to previous evidence regarding the role of the thyroid in risk for CA in offspring. Specifically, several studies have reported that the use of certain antithyroid medication (i.e., methimazole and pro-drug carbimazole) during pregnancy increases the risk of CA in offspring (Barwell et al., 2002; Barbero et al., 2008; Kannan et al., 2008; Clementi et al., 2010). In a study by Barbero et al. (2008), there was a strong positive association between methimazole use during pregnancy and CA among infants (OR, 17.75; 95% CI, 3.49–121.40). Methimazole, a suspected teratogen, readily crosses the placenta, and its use during pregnancy can lead to fetal hypothyroidism or underactive thyroid in the fetus (Shepard et al., 2002; Kannan et al., 2008). If maternal use of methimazole results in a thyroid hormone deficiency in the developing infant (Kannan et al., 2008; American Thyroid Association, 2012), our findings are consistent with a hypothesis that low thyroid hormone levels in embryos are associated with CA. However, it is more likely that low infant T_4 levels are a marker for another mechanism that is more directly involved in CA etiology. Furthermore, the possibility that the underlying maternal hyperthyroid condition, rather than maternal use of thyroid medication, may be contributing to the observed increased risk of CA has not been ruled out (Momotani et al., 1984; Barbero et al., 2008).

Our study should be considered in the light of certain limitations. CA is a relatively rare congenital malformation; therefore, our sample size was small (n = 69). However, despite this small sample size, we were able to detect significant associations between T_4 levels and CA. In addition, as CA develops early in pregnancy (i.e., 6–11 weeks' gestation), the infant's level of thyroid hormones at birth might not reflect the level of thyroid hormones during the critical period of development. Nevertheless,

Table 2
Adjusted Association between Infant Thyroxine (T_4) Levels and Choanal Atresia or Stenosis: Texas, 2004–2007[a]

	Infant T_4 level (μg/dL)	n (cases/controls)	Crude OR	95% CI	Adjusted OR[b]	95% CI
Continuous		69/3570	0.86	0.81–0.91	0.85	0.80–0.90
Quartiles						
1st	< 14.58	34/894	1.00	Reference	1.00	Reference
2nd	14.58 – 17.44	17/891	0.50	0.28–0.90	0.50	0.28–0.91
3rd	17.45 – 20.59	13/892	0.38	0.20–0.73	0.39	0.20–0.75
4th	≥ 20.60	5/893	0.15	0.06–0.38	0.15	0.06–0.40
p for trend			<0.001		<0.001	

[a]Nonsyndromic cases of choanal atresia or stenosis.
[b]Adjusted for gestational age and year of birth.
OR, odds ratio; CI, confidence interval.

this is an important first step in determining mechanisms related to CA development. Future studies assessing maternal T_4 levels in early pregnancy would be informative. Furthermore, our record of maternal medical condition and medication history may be incomplete, because such information is not routinely collected on vital records.

An important strength of our study is the use of a biochemical measure of exposure. We also examined the association among a relatively homogeneous sample by excluding infants with abnormal newborn conditions and syndromic cases of CA. Furthermore, we successfully linked the TBDR, one the largest birth defect registries in the United States with the statewide NBS data and conducted, to our knowledge, the first population-based study to examine the association between infant thyroid levels at birth and the risk of CA. Our study suggests that linking the NBS database to other population-based data is a useful strategy for assessing associations between infant biomarkers and risk of birth defects.

In summary, there was a significant association between low levels of thyroid hormones at birth and the risk of CA among infants with no known thyroid disease. Because little is known about the etiology of CA (Case and Mitchell, 2011), this is an important finding. In addition, our findings suggest that low thyroid hormone levels may have a role in the development of CA or that low infant T_4 levels at birth may be a marker for an embryonic process that is more directly involved in CA etiology. This is an exploratory study, and further study is needed to examine the role of thyroid hormones in the development of CA.

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