Clin Pediatr Endocrinol 2015; 24(2), 59–62

Short Communication

Advanced maternal age in Indian children with thyroid dysgenesis

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Abstract. A retrospective review of medical records of 80 children with thyroid dysgenesis (TD) was conducted to determine the association of gender and maternal age with TD. The study subjects were attending the Pediatric Endocrinology Clinic of our hospital which is a large tertiary care Multispecialty Pediatric Center located in Chandigarh, Northwest India. There were no gender differences (boys to girls' ratio 1:1). Mean maternal age of 25.87 ± 4.17 yrs (range 19–35 yrs) was significantly higher as compared to the mean maternal age of 23.87 ± 3.34 yrs (range 18–39 yrs) of a reference group ($p < 0.0001$). Odds of being older than 30 yrs were higher in mothers of children with TD as compared to mothers of normal children (OR 3.23; 95% CI: 1.54–6.44) (p-value 0.0003). In conclusion, our data shows that advanced maternal age is more prevalent in children with TD.

Key words: congenital hypothyroidism, thyroid dysgenesis, maternal age, gender differences

Introduction

Thyroid dysgenesis (TD) refers to the developmental defects of the thyroid gland that include aplasia, hypoplasia and ectopia, and accounts for majority of the cases of permanent congenital hypothyroidism (CH) in iodine sufficient regions (1). Although most cases of TD are sporadic, familial occurrence in about 2%, higher prevalence in certain ethnic groups like Hispanics and Caucasians, and in babies with Down syndrome suggest the possibility of a role of genetic factors in some cases (1, 2). Genetic mutations known to be associated with TD (TSHR, PAX8, NKX2-1, FOXE1, NKX2- 5 and PAX9) are, however, detected in only 2% of all cases (2). A possible role of factors like sexual dimorphism, parental consanguinity and advanced maternal age has also been proposed in some studies (3, 4). In the present study, we aimed to see if gender and maternal age have an association with TD in our patient cohort.

Received: September 16, 2014
Accepted: November 22, 2014
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Table 1 Age distribution of mothers of thyroid dysgenesis patients as compared to a reference population*

Age range (yrs)	Mothers of patients (%)	Control mothers* (%)	p value
< 20	3 (3.7)	99 (15.2)	0.005
20–30	63 (78.8)	510 (78.6)	0.967
>30	14 (17.5)	40 (6.1)	0.0002
Total	80 (100)	649 (100)	–

* reference cited (6).

Material and Methods

A retrospective evaluation of medical records of patients with CH due to TD followed up between 2004 and 2014 in the Pediatric Endocrinology Clinic of Advanced Pediatric Center, Chandigarh located in Northwest India, was performed. These children were referred from the general outpatient department of the hospital after obtaining a thyroid profile for symptoms suggestive of CH. Data related to age at diagnosis, gender, parental age, family history, thyroid scintigraphy, ultrasonography and thyroid hormonal levels were recorded. The diagnosis of TD was based on the findings of Technetium-99m pertechnetate thyroid scintiscan and thyroid ultrasonograms done at the time of initial evaluation of CH. The diagnosis of hypothyroidism was based on low serum total T4 levels and elevated serum TSH levels according to reference ranges (5). Those having subclinical hypothyroidism, autoimmune thyroiditis or syndromic diagnosis like Down syndrome (DS) were excluded. Maternal and paternal ages at the time of child birth were determined by subtracting the child's age from the parental ages at the time of diagnosis. Maternal ages were compared with the normative data presented in a previous Indian study (6).

The logistic regression analysis was performed to find out the independent predictive ability of maternal age for the binary outcome of TD. Pearson's correlation was used to analyse correlations among various quantitative study variables investigated. Comparisons of maternal ages with normative data were made by the student's independent t-test. A p-value of ≤ 0.05 was considered as statistically significant. All the statistical analyses were performed on Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 18.0 for Windows).

Results

Complete information on thyroid scintigraphy and ultrasonography was available in 80 out of 310 children referred to our Pediatric Endocrinology Clinic with a diagnosis of CH over the study period. Majority (63, 78.7%) had agenesis of thyroid gland followed by ectopic gland in 12 (15%) and hypoplasia in 5 (6.2%) patients. In ultrasound, agenesis was detected in 70 (87.5%) and ectopia and hypoplasia each in 5 (6.2%) patients. There were 40 (50%) boys and 40 (50%) girls (male to female ratio 1:1). They were born at term gestation and had average birth weights. Their mean age (SD) at diagnosis was 2.65 (2.81) yrs (range 2 mo to 11 yrs). The mean initial total T4 and TSH concentrations in these children were 2.705 ± 2.384 µg/dL (range 0.01–8.9) and 293.48 ± 289.81 mIU/L (range 10.03–1159.0) respectively. Mean maternal age (SD) of 25.87 (4.17) yrs (range 19–35 yrs) was significantly higher as compared with the mean maternal age (SD) of 23.87 (3.34) yrs (range 18–39 yrs) in a reference population ($p < 0.0001$) (6). Although majority (82.5%) of mothers were less than 30 yrs of age at the time of birth of

the child with TD, 17.5% were older than 30 yrs as compared to only 6.1% in the cited reference (Table 1). Odds of being older than 30 yrs were 3.23 times higher in mothers of children with TD as compared to mothers of normal children (OR 3.23; 95% CI: 1.54–6.44) (p-value 0.0003). This gives an attributable fraction of 12% in population which means that 12% of TD can be eradicated by eliminating risk factor of older maternal age (> 30 years) at childbirth. However, the mean maternal age in the present study was lower than the mean maternal age (27.8 ± 5.4 yrs, range 18–43 yrs) of our cohort of children with thyroid dysfunction associated with DS (7).

Mean paternal age in our patients was similar to a reference population of a previous study from India (29.60 ± 4.33 yrs, range 22–38 yrs versus 29.3 ± 5.4 yrs, range 20.0–42.0 yrs, p-value 0.65) (8).

Discussion

The present study aimed to investigate the association of gender and maternal age with TD, the commonest cause of CH in our set up. No gender differences were observed in our patient cohort similar to a previous study (4). Gender differences have been suggested to modulate thyroid gland development during fetal period probably involving molecular mechanisms (3). The higher prevalence of TD in girls, however, has not been consistently reported (2).

Our data indicates that advanced maternal age was more common in children with TD. These findings are similar to a previous study in Turkish patients (4). Although advanced maternal age is a risk factor for numerous maternal and fetal conditions (9), the reasons for its association with TD are presently unknown. Age-related decreases in meiotic cohesins leading to increased segregation errors and oocyte aneuploidy are associated with several congenital birth defects (10). However, oocyte aneuploidy does not appear to be a factor in our study as children with chromosomal abnormalities were excluded. In a previous study, it was proposed that advanced maternal age may increase the risk of mutations in genes encoding some transcription factors associated with thyroid gland development (4). But acquisitions of intragenic mutation are more frequently observed in the paternal allele, and the frequencies of the events generally correlate with paternal age. In this context, further large studies are required to confirm the observed association with advanced maternal age and then elucidate the underlying mechanisms contributing to TD.

In conclusion, our study shows that advanced maternal age is more prevalent in children with TD and this may be one of the several risk factors associated with thyroid developmental defects.

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