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Research Article

Evidence of Thyroid Autoimmunity in Patients with Congenital Hypothyroidism Due to Thyroid Dysgenesis or Dyshormonogenesis

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Abstract

Background: Congenital hypothyroidism (CH) is caused by thyroid dysgenesis (TD) or thyroid dyshormonogenesis (TDH) which are not autoimmune conditions. TD can be sporadic or rarely due to genetic mutations. TDH occurs due to defects in thyroid hormone synthesis. The coexistence of autoimmunity in TD and TDH cases has rarely been described.

Objective: To evaluate evidence of autoimmunity in patients with TD and TDH. To assess the impact of autoimmunity on a successful trial off in TDH patients after 3 years of age.

Methods: Retrospective chart review of patients diagnosed with CH. Demographics, family history, biochemical (TSH and FT4) and radiologic studies to evaluate thyroid function were reviewed. Presence of thyroid antibodies (TAb) at time of diagnosis and/or at ≥ 3 years of age in CH patients were assessed. All variables were analyzed and compared in both groups (TD and TDH).

Results: A total of 50 patients were included, 38 (76%) with TDH and 12 (24%) with TD. Among all cases, 11 patients (22%) had positive TAb. In TDH group, 9 subjects had positive TAb (5 with TgAb, 4 with TPOAb). In TD group, 2 patients were demonstrated to have thyroid autoimmunity (TPOAb in a patient with athyreosis and TgAb in a patient with ectopic thyroid).

Conclusion: A subset of patients with CH can have presence of TAb and may contribute to continuous need for TRT. Disturbances in thyroid structure or function may predispose to development of thyroid autoimmunity in CH. Future studies should examine this relationship using a prospective design.

Keywords: *Congenital Hypothyroidism; Thyroid Dysgenesis; Thyroid Dyshormonogenesis; Thyroid Antibodies; Thyroperoxidase Antibody; Thyroglobulin Antibody*

Introduction

Congenital hypothyroidism (CH) is defined as thyroid hormone deficiency present at birth which is most commonly caused by a problem with thyroid gland development, thyroid dysgenesis (TD) or a disorder of thyroid hormone biosynthesis, dyshormonogenesis (TDH). These types of CH results in primary hypothyroidism and do not have an autoimmunity etiology, hence antithyroid antibodies are typically absent. TDH accounts for 10 - 15% of primary CH and TD for 85% of the cases and presents in three major forms: thyroid ectopy, athyreosis and thyroid hypoplasia. Both TD and TDH can be sporadic or due to genetic mutations which are not autoimmune conditions [1].

Thyroid hormones are essential for the development of the central nervous system (CNS) because they play a role in neurogenesis and specific neurotransmitter regulation, hence early thyroid replacement is recommended and Levothyroxine (LT4) is the treatment of choice. If permanent congenital hypothyroidism has not been established by two to three years of age the AAP and the ESPE recommend a 30 day trial off l-thyroxine therapy [2,3]. The authors of this study incidentally found presence of thyroid autoimmunity in a patient with thyroid agenesis and poorly controlled disease, leading to the hypothesis if concomitant presence of thyroid autoimmunity in cases of CH could predispose to poorly control disease or fail in trial off LT4 in patients with TDH.

Materials and Methods

The objective of the study was to evaluate the evidence of thyroid autoimmunity in patients with TD and TDH and to assess the impact of such autoimmunity on a successful trial off in TDH patients after 3 years of age. Study subjects consisted of patients with diagnosis of CH that follow in the Pediatric Endocrinology outpatient clinics at Bellevue and New York University Langone Hospital from January 2014 to July 2018. Study was IRB approved. Demographics, family history, biochemical and radiologic studies to evaluate thyroid function were retrospectively reviewed. Subjects were examined by sex, age, thyroid stimulating hormone (TSH) and free T_4 (Table 1). Hypothyroidism was defined by low levels of free T_4 by age, and an elevated TSH level. The etiology of congenital hypothyroidism was determined by thyroid ultrasonography. Presence of thyroid autoimmunity was examined by evaluating the existence of positive Thyroperoxidase (TPOAb) and/or Thyroglobulin antibodies (TgAb) at time of diagnosis and/or at ≥ 3 years of age in TD and TDH patients. Trial off levothyroxine (LT4) was attempted at 3 years of age in patients with TDH (Table 1). The disease control in patients with TD and TDH as well as success of trial off LT4 in patients with TDH was determined based on normal TSH and free T_4 by age.

	Thyroid Dyshormonogenesis (TDH)	Thyroid Dysgenesis (TD)
Total	38	12
Sex		
Male	30	4
Female	8	8
At diagnosis		
Age (days)	34 +/- 3.37	19 +/- 5.65
TSH (mean +/- SD)	53 +/- 17.82	241 +/- 68.22
Free T4 (mean +/- SD)	1.17 +/- 0.07	0.87 +/- 0.13
Thyroid Ultrasound		
Normal	38/38	0/12
Ectopic gland	0	5
Partial Dysgenesis	0	3
Complete Dysgenesis	0	4
Knee X-ray		
Performed	20/38	6/12
Normal	20	4
Delayed bone maturation	0	2

Family History of hypothyroidism	18/38	4/12
Mother	3	1
Father	1	0
Siblings	11	1
Other	3	2
Maternal hypothyroidism Causes	3/38	1/12
Maternal TDH	1/3	0/1
Maternal Autoimmunity	2/3	1/1
TPOAb and TgAb in off-spring	0/3	0/1

Table 1: *Demographics and clinical data in patients with congenital hypothyroidism.*

Results

A total of 50 patients were included, 38 (76%) with TDH and 12 (24%) with TD. Among all CH cases, 11 patients (22%) had positive thyroid antibodies (9 with TDH and 2 with TD).

TDH group: 38 patients were included in this group. At time of diagnosis, the patients were 34 +/- 3.37 days old with TSH of 53 +/- 17.82 uIU/mL (N 0.35 - 4.8 uIU/mL) and FT4 of 1.17+/0.07ng/dL (N 0.9 - 1.9 ng/dL), and were started on TRT (mean 25 mcg). All had negative thyroid antibodies, normal thyroid US and normal epiphysial maturation on x-ray (XR) knee.

A trial off TRT was attempted in 18 patients after 3 yrs of age (3.9 +/- 0.29 yrs) with TSH of 3.30 +/- 0.25 uIU/mL and FT4 1.35 +/- 0.039 ng/dL; 11 passed and 7 failed the trial. Thus 27/38 patients continued to be on TRT (7 who failed the trial off and 20 in which trial off was not possible due to high dose of TRT and intermittent elevated TSH), 33% (9/27) had positive thyroid antibodies (5 with TgAb, 4 with TPOAb).

TD group: At time of diagnosis, the patients were 19 +/- 5.65 days old, had TSH of 241 +/- 68.22 uIU/mL and FT4 of 0.87 +/- 0.13 ng/dl, they were all started on TRT. Thyroid US showed 5 cases with ectopia, 4 agenesis and 3 partial dysgenesis. Two patients had delayed epiphysial maturation on XR knee. Among all cases with TD, 17% (2/12) had positive thyroid antibodies (TPOAb in agenesis and TgAb in ectopic thyroid).

The majority of patients with positive thyroid antibodies 10/11 patients (91%) continued to required TRT (Table 2).

	Thyroid Dyshormonogenesis (TDH)	Thyroid Dysgenesis (TD)
N=	38	12
Trial off	18	0
Passed	11	
Failed	7	
Not performed	20	
Age (years)	3.9 +/- 0.29	n/a
TSH	3.30 +/- 0.25	n/a
FT4	1.35 +/- 0.03	n/a
Any Thyroid Ab positive	9	2
Positive TPO Ab	4	1
Passed trial off	1	0
Fail trial off	1	0
Trial not performed	2	1
Positive Tg Ab	5	1
Passed trial off	0	0
Fail trial off	3	0
Trial not performed	2	1

Table 2: *Analysis of thyroid status in congenital hypothyroidism at 3 years of age.*

Discussion

Primary congenital hypothyroidism (CH) is defined as the condition resulting from thyroid hormone deficiency present at birth and caused by abnormalities in thyroid gland formation or function. The most common cause of primary CH is abnormal development of the thyroid gland (thyroid dysgenesis, TD) in 85% of cases. A defect in the normal production of thyroid hormones due to defects in enzymes and ion transporters (thyroid dyshormonogenesis, TDH) corresponds to approximately 10% to 15% of the cases [1]. However, in our study we noticed a preponderance of TDH in 75% of the patients, in contrary to TD seen in only 25% of the cases, likely because we included only CH patients who had TAb measurements which could have led to differences in the distribution of known etiologies.

It is known that TD and TDH do not have an autoimmunity etiology, hence thyroid antibodies (TAb) are typically absent. However, the authors found clinical and biochemical evidence of autoimmunity by presence of thyroid Delphian Lymph node in a patient with thyroid agenesis and poorly controlled hypothyroidism, prompting evaluation for concomitant thyroid autoimmunity and demonstrating presence of positive Tab, this event raised the question if coexistent autoimmunity in cases of TD and TDH (although rarely described) could be a contributing factor to failing trial off Levothyroxine (LT4) at 3 years of age in patients with TDH or having a poorly controlled disease in patients with TD and TDH and only few studies have examined the coexistence of thyroid autoimmunity in patients with congenital hypothyroidism due to TD and TDH, Wooko., *et al.* in 2013 and Ruchala., *et al.* in 2016 [4,5].

Autoimmune thyroid disease (AITD) is defined as abnormal thyroid function causing hyper or hypothyroidism in presence of positive thyroid antibodies. AITD is thought to be caused by a combination of genetic susceptibility and environmental factors. Both thyroid-specific genes and genes involved in immune recognition and/or response have been identified [6,7].

Association of thyroid dyshormonogenesis or dysgenesis with autoimmunity

Wooko., *et al.* in 2013 studied the presence of AITD evidenced by positive TgAb in patients with non-transient CH. A total of 60 children with CH (26 boys and 34 girls) with mean age 8.4 ± 3.8 years were studied. Control group involved a total of 45 patients (30 boys and 15 girls), mean age 3.1 ± 3.3 years. The causes of CH were TDH in 26 patients (59%), thyroid dysgenesis in 13 patients (30%), thyroid agenesis in 4 patients (9%), and ectopic thyroid in a 1 patient (2%) and 16 were unidentified. Patients in the CH group had significantly higher ($P < 0.001$) TSH and TgAb levels (TSH 63.6 ± 32.3 μIU/mL and TgAb 119.4 ± 34.7) compared to the control group (TSH 2.9 ± 2.3 and TgAb 80.6 ± 19.6). Although TgAb could be seen in about 11% of normal individuals, the authors of this study were able to identify a significant increase of TgAb in the group with CH regardless of different causes. The author proposed that it could be due to antigenicity related to thyroid tissue or proteins [4].

In our study we examined the presence of coexistent autoimmunity in patients with primary CH. Besides TgAb, we also tested TPOAb. Among all CH cases (50 patients), 11 cases (22%) had positive thyroid antibodies. In the TDH group, 9 subjects had positive TAb (4 TPOAb and 5 TgAb). In the TD group, 2 patients had positive TAb (TPOAb in a patient with athyreosis and TgAb in a patient with ectopic thyroid).

TD can present as ectopia, partial dysgenesis (hemiagenesis) or total dysgenesis (agenesis) of the thyroid, most of the cases are sporadic, however, some mutations in the genes programming transcription factors involved in thyroid gland development have been described in approximately 2% of these cases [8].

AITD involving ectopic thyroid tissue (ETT) is particularly unusual and has been rarely reported. Some reports have described coexistence of autoimmunity and ETT. We found in Pubmed 8 reported cases of thyroid ectopia with associated thyroid autoimmunity, 7 female (4 children and 3 adults) as well as 2 adult male cases [9-16]. Similarly, in our study we describe 5 patients with ectopic thyroid (4 lingual and 1 suprasternal) and thyroid autoimmunity was found in 1 case with positive TgAb.

Thyroid hemiagenesis (THA) may have concomitant occurrence of autoimmunity. Ruchala., *et al.* in 2016 studied the thyroid autoimmunity incidence in patients with THA and influence of higher than average TSH level on thyroid volume (TV) and its change with age. In the studied and control group the presence of TAb was evaluated. The THA group consisted of 65 patients (56 women and 9 men) with mean age of 40.9 ± 19.7 years. The control group consisted of 65 age matched patients with normal bilobate thyroid. In the study group 53.85% ($n = 35$) of patients had elevated serum concentration of at least one type of TAb. Increased levels of TPOAb were found in 31, TgAb in 16, and TRAb in 11 cases, respectively. In the control group only 9 of 65 subjects (13.85%) had increased titer of TPOAb, TgAb or TRAb [5]. It must be stressed that AITD its more preponderant in adult population. Indeed, in our study we included 2 children with THA that had negative TAb.

Thyroid agenesis (TA) with concomitant thyroid autoimmunity has rarely been described as thyroid tissue is typically absent. Of interest Wooko., *et al.* described as part of their study 3 out of 4 patient with thyroid agenesis had indeed had highest titers of TgAb [4]. In our study 4 patients had thyroid agenesis and 1 of them (our sentinel case) had positive TPOAb and negative TgAb.

Trial off TRT was performed at 3 years of age only in TDH patients with normal TSH and Free T4 levels (47%), in the remaining 53% the trial was not attempted given due to high dose of TRT and intermittent elevated TSH. Overall, 71% of TDH patients continued on TRT of which 33% had evidence of AITD. Our observation, although in small sample study, implies the possibility of coexistence of autoimmunity may exist in TDH. Whereas in cases of TD, trial off TRT was not done as they have continuous need of TRT, however knowledge of

associated AITD may guide TRT dose adjustments. Thus far, there is no data examining the relationship of success of trial of LT4 in given population.

Factors possibly leading to thyroid autoimmunity in congenital hypothyroidism due to TD and TDH

The main biochemical feature of thyroid autoimmunity is the presence of anti-thyroid antibodies in bloodstream against the two major thyroid antigens, microsomal antibody also known as thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgA).

Thyroglobulin (Tg) is the main component of thyroid follicular colloid [17].

Posttranslational modifications and the amount of the iodination are the most important determinants of Tg immunogenicity. Highly iodinated Tg has been found to be more antigenic [18] and could be responsible for the elevation of TgAb titer which can occur with and without thyroid tissue destruction.

Thyroperoxidase (TPO), the primary enzyme involved in thyroid hormonogenesis is a heme containing oxidoreductase and a membrane-spanning glycoprotein located on the apical surface of thyrocytes. TPO is one of the main autoantigens involved in autoimmune thyroid diseases (TPOAb) which can activate complement and are capable of inducing antibody dependent cell-mediated cytotoxicity causing thyroid cells destruction [19].

Autoimmune thyroid disease (AITD) arises due to complex interactions between exogenous and endogenous factors.

The exogenous factors that have been suggested are *bacterial and* viral infections which due to specific cytokines can promote the development of AITD [20-22], *high oral Iodine intake* (~400 - 600 µg/day) which increases the immunogenicity of Tg by creating new epitopes or unmasking cryptic epitopes, increasing TPOAb in the general population from 14.3 to 23.8% and for TgAb from 13.7 to 19.9% [23,24], Environmental exposures (polyaromatic hydrocarbons, polychlorinated biphenyls and polyhalogenated biphenyls) has been postulated to cause elevation in TPOAb and TgAb [25], drugs like amiodarone and lithium [26], Radiation which may induce thyrocyte damage and stimulate the release of thyroid antigens [27-30], and vitamin D deficiency. Some studies have detected a significant negative correlation between serum 25 (OH) vitamin D and TPO Ab levels but the association between vitamin D levels and AITD is still a conflicting topic. Although the precise environmental trigger has not been yet established an epigenetic mechanism may be [28].

The endogenous factors that have been proposed to cause thyroid autoimmunity are mainly sex and genetic disposition. AITD has a striking predilection for females, but in prepubertal age the female/male ratio is lower. It has been proposed that females have similar numbers of lymphocytes but higher antibody production by B cells and stronger humoral and cellular immune responses [31]. One reason for the observed differences might be the prominent immune modulatory effects of estrogens [32]. Interestingly in our study we didn't find any female preponderance likely because the females in our study were in prepubertal age at which point the estrogen levels are lower and the female/male ratio for AITD is lower.

Endogenous genetic factors have been implicate din AITD and two types of genes have been described, immunomodulatory genes (*HLA-DR*, *CTLA-4*, *PTPN22)* and thyroid specific genes (*TPO, NIS*, *Duox2*, thyroglobulin, TSH receptor) [33-35] which work on inter- and intra-cellular level regulating normal hormone synthesis and have been implicated in pathogenesis and thyroid dysfunction as well as determining susceptibility to thyroid autoimmunity. It has been postulated that family history of AITD is seen in 30% to 40% of patients. A study about familial clustering of juvenile AITD found TAb detectable in 56% of mothers and 25% of fathers. Interestingly, HLA DQ alleles and antibody status in fathers influenced the susceptibility to AITD in children. Siblings recurrence in childhood was determined to be 20 - 30% [36,37]. Indeed, among the 11 patients in our study that presented coexistent positive antibodies, 3 of them have family history of positive thyroid antibody (all in siblings).

As for the mechanism of development of AITD in TD or TDH, it has been proposed by Wooko., *et al.* [4] that excessive stimulation of TSH receptors caused by high TSH may induce a "leak" of some thyroid autoantigens that may induce an autoimmune response. Similarly, we believe that patients with TD or TDH may also have a background inherited predisposition to autoimmunity with additional environmental and hormonal factors that trigger or contribute to the development of AITD.

There are some limitations in our study. First, is the retrospective design of the study which may have omitted some patients with CH and was not able to evaluate compliance with TRT. Second, many infants with CH were not included because TAb testing had not been performed leading to a small sample size. Third, in the CH patients that had TGAb and TPOAb, these were qualitatively assessed and we believe that quantitative measurement of these using same metrics may yield more precise information. Fourth, the TRT the patients received varied by manufacturers (generic versus brand) which could have led to different levels of control of the disease. Another limitation is that our study cohort did not undergo TSH receptor Antibody measurement neither genetic analysis. Also, we did not study possible exogenous or environmental contributors to thyroid autoimmunity.

Conclusion

A small subset of patients with CH can have concomitant presence of thyroid Ab which may contribute to continuous need for thyroid hormone replacement. Disturbances in thyroid structure or function may predispose to development of thyroid autoimmunity in CH. Furthermore, future prospective studies should examine this relationship and its clinical significance.

Conflict of Interest

The authors have no financial or other relationships the could lead to a conflict of interest.

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Volume 9 Issue 8 August 2020