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Thyroid Abnormalities among First-Degree Relatives of Children with Congenital Hypothyroidism: An Ultrasound Survey

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Key Words
Congenital hypothyroidism · First-degree relative · Thyroid abnormality · Thyroid gland · Ultrasonography

Abstract
Background: Congenital hypothyroidism (CH) is caused by thyroid dysgenesis and dyshormonogenesis. Evidence suggests the presence of genetic factors in both types of pathogenesis. We investigated whether an increased incidence of thyroid abnormalities could be shown by ultrasonography among first-degree relatives of children with CH. ***Material and Methods:*** In this case-control study the presence of both developmental and non-developmental thyroid abnormalities was studied among first-degree relatives of CH patients and healthy children. Assessments included neck ultrasonography and thyroid function tests. The data obtained from parents, siblings and children were compared in the case and control groups. ***Results:*** In the case group, 92 patients, 172 parents and 57 siblings, and in the control group, 82 healthy children, 160 parents and 39 siblings were studied. Thyroid developmental abnormalities were more prevalent among parents (3.5 vs. 0%, p = 0.03) and siblings (10.5 vs. 0, p = 0.01) of CH patients than the control group. Non-developmental abnormalities were not significantly different between the case and control groups (17 vs. 13%, p = 0.3). ***Conclusion:*** Thyroid developmental abnormalities were more prevalent among parents and siblings of CH patients than the control group, confirming the familial component of this entity.

Introduction

Congenital hypothyroidism (CH) affects about 1: 3,000–4,000 infants and may be caused by defects in thyroidal ontogeny or hormone synthesis [1, 2]. Thyroid dysgenesis (TD) can be responsible for up to 85% of CH patients [3, 4]. It includes thyroid agenesis, ectopic thyroid tissue, thyroid hypoplasia and thyroid hemiagenesis [5, 6]. The pathogenesis of TD is not known. The possible role of autoimmune or unidentified environmental factors has been suggested, but not confirmed [7–9]. In the remaining 15%, CH is associated with congenital goiter and results in dyshormonogenesis, with a defect in one of the biochemical mechanisms being responsible for thyroid hormone synthesis [10]. In these cases, the disease is transmitted in the autosomal recessive mode and a wide spectrum of mutations has been identified [11].

TD is usually regarded as being sporadic with a female predominance [6, 11], but recent cohort analyses have es-

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timated that the number of familial cases is 15-fold higher than what would be expected by chance alone, confirming the existence of a strong familial component in CH due to TD. The coexistence of CH cases with a normal sited gland and CH due to TD in some families has been reported [5, 6]. In some cases of CH, evidence has suggested a multifactorial origin, including genetic and environmental factors [12]. The higher prevalence of CH in girls and some ethnic groups, and a higher prevalence of extrathyroidal congenital anomalies among infants with CH compared with the general population suggest the presence of genetic factors in the pathogenesis of CH [13–17].

Evidence indicates that among first-degree relatives of a CH population with TD, there is an elevated rate of asymptomatic thyroid developmental anomalies when they are systematically screened by ultrasound [18]. It is reported that thyroid gland abnormalities (non-developmental), such as goiter, are also more frequent among mothers of infants with CH [19]. It therefore seems possible that a common underlying mechanism exists for both etiological groups [6].

With an incidence of 1/370, CH is not a rare condition in the Province of Isfahan [20], and the families from this region form a large risk population for thyroid abnormalities. Taking all the previously demonstrated data into consideration, we aimed to investigate whether an increased incidence of thyroid abnormalities could be shown by ultrasonography among first-degree relatives of CH patients.

Materials and Methods

This was a case-control study on first-degree relatives of children with confirmed CH. From May 2002, T4 and TSH serum concentrations of all 3- to 7-day-old newborns, born in all 17 hospitals of the city of Isfahan, were measured by radioimmunoassay (RIA) and immunoradiometric assay (IRMA), respectively, using Kavoshyar (Iran, Tehran) kits. The newborns with abnormal screening results were re-examined and newborns with an abnormal T4 and TSH level at second measurement were diagnosed as being CH patients and received treatment and regular follow-up [20].

We invited the parents and siblings of 100 CH patients during their routine follow-up in Isfahan Metabolism and Endocrine Research Center (case group). 100 of the first relatives of children with normal screening results were invited as well (control group). Assessments included neck ultrasonography and thyroid function tests in all subjects. Written consent was obtained from the parents, and serum TSH and T4 concentrations were measured in the first-degree relatives of CH and healthy children by IRMA and RIA methods respectively. Thyroid function tests were performed in our Research Center Laboratory using Berthold-LB2111 unit gamma counter equipment.

Thyroid ultrasonography was performed and interpreted by the same method described by Léger et al. [18]. The same equipment with a HLS-475M, 7.5-MHz linear transducer (HS-Honda 2000, Japan) was administered. Images were obtained in the transverse and longitudinal planes with subjects in the supine position and hyperextended neck. The radiologist looked for the presence or absence of thyroid glands at the normal location, presence or absence of the isthmus and each lateral thyroid lobe and their shape, and any additional thyroid tissue. Agenesis was defined when a normal thyroid gland was not found in the cervical location; if there was no thyroid gland in the normal location but some thyroid tissue in the midline of the neck, it was defined as ectopia. These were confirmed by scintiscan in CH patients. The anterior cervical area was systematically studied for the persistence of part of the thyroglossal duct from the foramen cecum to the normal anatomic position of the thyroid gland and even lower above the sternal manubrium.

The presence of the pyramidal lobe representing the persistence of the caudal portion of the thyroglossal duct was also assessed. It usually lies in the midline attached to the thyroid gland but can arise from either lobe (more commonly from the left lobe). The volume of the thyroid gland was assessed in each individual and the presence of simple goiter (according to the WHO recommended normative values for thyroid volume in children and adults) [21, 22], multinodular goiter, nodule, colloid cyst and thyroiditis was demonstrated as non-developmental thyroid abnormalities. The presence of agenesis, hemiagenesis and ectopia was demonstrated as developmental thyroid abnormalities.

The data obtained from parents, siblings and children were compared between the case and control groups. Data were analyzed using SPSS-13 software and Fisher's exact test, t test and χ^2 test.

Results

Ninety-two (92%) families in the case group and 82 (82%) in the control group responded to our invitation. The case group population consisted of 92 CH patients (female/male = 38/54), 172 parents and 57 siblings (29 boys and 28 girls). According to the results of ultrasonography, 49 (53.3%) of CH patients had thyroid dysgenesia and 43 (46.7%) had normal thyroid gland. Among CH patients with dysgenesia, 38 had agenesia (female/male = 20/18), 7 had hemiagenesis (female/male = 4/3), and 4 had ectopia (female/male = 1/3). The control group population consisted of 82 healthy children (female/male = 34/48), 160 parents and 39 siblings (19 boys and 20 girls). According to the results of ultrasonography, all children studied in the control group had a normal sited thyroid gland.

The presence of thyroid gland abnormalities (developmental and non-developmental) among parents and sib-

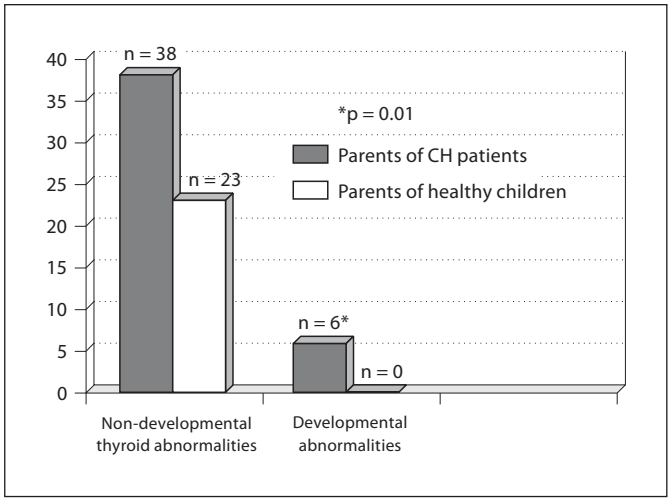

Fig. 1. Prevalence of thyroid gland abnormalities, developmental and non-developmental, among parents of CH and healthy children.

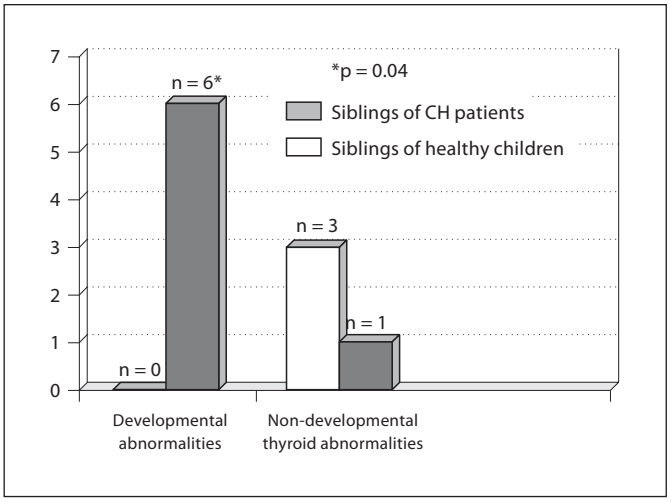

Fig. 2. Prevalence of thyroid gland abnormalities, developmental and non-developmental, among siblings of CH and healthy children.

lings of CH patients and healthy children are presented in figures 1 and 2. The presence of non-developmental thyroid abnormalities such as goiter, multinodular goiter, thyroid nodule, colloid cyst and thyroiditis were not different among the case and control groups (39/229 in case group vs. 26/199 in control group, $p = 0.3$). The overall prevalence of thyroid developmental abnormalities in relatives of our CH patients was 5.2% with parents (6/172) and siblings (6/57), 3.5 and 10.5% respectively. There were no thyroidal developmental abnormalities among the control group in either parents or siblings ($p < 0.05$).

The 6 parents with developmental abnormalities were mothers affected with hemiagenesis and 6 siblings had developmental thyroidal abnormalities; 2 brothers and 1 sister had absence of cervical thyroid gland and 3 sisters had hemiagenesis. Therefore, 75% (9/12) of the reported developmental thyroidal abnormalities were hemiagenesis in these relatives.

Four mothers and 5 siblings (2 brothers and 3 sisters) with thyroid developmental abnormalities were relatives of CH patients with TD. The remainder (2 mothers and 1 sister) were parents and siblings of CH patients with a normal sited thyroid gland.

Of 6 mothers with thyroid developmental abnormalities, 2 were mothers of 2 CH patients (1 male and 1 female) with agenesis, 2 were mothers of 2 CH patients (1 male and 1 female) with hemiagenesis, and 2 others were mothers of 2 CH patients (1 male and 1 female) with a normal sited thyroid gland.

Two brothers with thyroid developmental abnormalities were brothers of 2 CH patients (1 male and 1 female) with agenesis.

Of 4 sisters, 2 were sisters of 2 CH patients (1 male and 1 female) with agenesis, 1 was a sister of a CH patient (male) with hemiagenesis and the other one was a sister of a CH patient (female) with a normal sited thyroid gland. The prevalence of thyroid developmental abnormalities in relatives (siblings, n = 28 and parents, n = 89) of TD patients was 7.7% (9/117).

There was no difference in serum T4 and TSH levels and calculated thyroid volumes in parents and siblings of the case and control groups (table 1).

Discussion

This study shows that the frequency of thyroid gland developmental abnormalities was higher among parents and siblings of CH patients than the normal population. Thyroid developmental abnormalities were present among 3.5% of parents of CH patients and 10.5% of their siblings, whereas there were no thyroidal developmental abnormalities among the control group.

The overall prevalence of thyroid developmental abnormalities (5.2%) in the relatives of our CH patients was lower than the results of Léger et al. [18]. They reported that 7.9% of TD families and 0.9% of the control group had thyroid developmental abnormalities, and concluded

Table 1. Characteristics of CH and healthy children and their parents and siblings

	Children		Siblings		Parents	
	cases (n = 92)	controls (n = 82)	cases (n = 57)	controls (n = 37)	cases (n = 172)	controls (n = 160)
Age	21.1 ± 9.6 months p = 0.8	22.2 ± 9.6 months	9.8 ± 3.4 years p = 0.2	10.6 ± 4.5 years	29.05 ± 5.4 years p = 0.8	29.9 ± 5.8 years
TSH, mIU/l	78.1(5.8–492.0) p < 0.05	1.9 (0.1–18.9)	2.9 (0.1–31.7) p = 0.2	2.5 (0.7–88.6)	2.1 (0.1–64.1) p = 0.1	1.8 (0.1–10.3)
T4, μg/dl	4.9 ± 3.5 (p < 0.05)	10.8 ± 2.3	8.8 ± 1.7 p = 0.5	8.7 ± 1.3	7.9 (3.8–13.9) p = 0.3	7.7 (2.5–96.0)
Thyroid volume mm^3	0.4 (0.08–2.0) p < 0.05	1.1 (0.3–2.3)	2.6 (0.3–15.9) p = 0.07	3.55 (0.7–10.3)	8.9 (0.5–36.8) p = 0.08	8.1 (1.3–21.5)

Data are presented as median (min–max). T4 normal range: 4.5–12 μg/dl. TSH normal range: 0.3–3.9 mIU/l.

that thyroid developmental abnormalities are compatible with an autosomal dominant mode of inheritance with a low prevalence estimated at 21% for symptomatic thyroid developmental abnormalities and a probability of <7% of developing CH for a carrier of the susceptibility allele [18]. They studied CH patients with dysgenesis and their relatives, but we studied the relatives of all CH patients during their 3 years of follow-up and treatment, which could explain this difference.

According to our ultrasonographic results, the prevalence of these abnormalities among relatives of CH patients with dysgenesis was 7.7%, which was similar to their results. According to the guidelines of our CH screening program, these CH patients should be treated and followed up for 3 years and then treatment would be discontinued for 4–6 weeks. Afterwards, according to their thyroid function test and thyroid scintigraphy and/or ultrasonography, they would be classified as permanent CH with two etiologies of dysgenesis and dyshormonogenesis and transient CH [23]. Therefore, CH patients whose thyroid ultrasonography revealed a normal thyroid gland are consistent with those with dyshormonogenesis or transient CH, so we were unable to determine the prevalence of thyroid developmental abnormalities in dyshormonogenetic CH patients. The exact conclusion about the relation of these abnormalities and etiologies of CH will be determined in the future after 3 years of follow-up.

In our study, 75% of the reported thyroid developmental abnormalities were thyroid hemiagenesis and not other abnormalities that were reported by Léger et al. [18]. It may be due to different ethnical variations or the small sample size. Thyroid hemiagenesis is reported to be a rare form of TD which can occur as a familial disorder and can be associated with any form of TD. Most subjects with this abnormality present with subclinical hypothyroidism [24]. The high prevalence of thyroid hemiagenesis in our study can be due do genetic factors resulting from parental consanguinity marriages which frequently occur in this region [25]. Our observations, in accordance with the studies in this field [5, 6, 18], support the hypothesis of genetic components of TD, and suggest an association between asymptomatic hemiagenesis and TD, confirming previous genetic hypotheses.

The sex ratio was different from what has previously been reported [25]. This may show that boys were more likely to be referred to the clinic than girls and might be due to the non-random nature of our sampling method. As we did not aim to investigate the sex distribution among CH patients, this should be studied in another study. Anyhow, females are more likely to show CH and TD. It can be said that if we had more females we would have more thyroid dyshormonogenesis and TD, and thus would see more hereditary patterns [13–17].

The presence of non-developmental thyroid abnormalities, such as goiter, multinodular goiter, nodule, colloid cyst and thyroiditis, was not different among the case and control groups. Several studies have reported different results in this field. Sunartini and Nakamura [19] studied the thyroid function in newborn infants from goitrous and non-goitrous mothers; they reported that 2 cases of CH patients were found in infants of goitrous mothers. On the other hand, as in our study, Glinoer et al. [26] in their study on pregnancy in patients with mild

thyroid abnormality, such as goiter, nodules and thyroid autoantibodies, reported that thyroid function in newborns from mothers with thyroid abnormalities was normal and not different from that in controls. However, considering that goiter and other non-developmental abnormalities are related to environmental and autoimmune factors and also the role of these factors on CH [7–9], it is recommended that more studies in this field are needed in order to study the rate of autoimmunity and thyroid disorders in relation with the CH etiologies mentioned earlier.

The CH screening program in Isfahan was started 2002, so the mean age of the CH children we studied was 21–22 months, which was lower than the mean age of their siblings. 53/92 of the CH patients we studied were the first born child of the families, so the sample size of the siblings was smaller and the reported mean age of siblings was more than CH patients in the case group. In other words, most of our CH patients were the only or the last child of their families.

In conclusion, the present study which confirms the familial component of thyroid developmental anomalies and the possible underlying mechanism of non-developmental anomalies, points to the genetic basis of the disease and provides insights for further genetic studies in this field. However, for a more accurate conclusion, considering that CH has a multifactorial basis, further studies are needed on selected cases of CH with TD or dyshormonogenesis etiology which would clarify the role of family history and genetics in each etiology.

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