

Thyroid dysgenesis as a risk factor for patients with poorly controlled congenital hypothyroidism

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Objective

Our aim was to search for the risk factors of cases with poor controlled congenital hypothyroidism (CH) in correspondence to their clinical aspect.

Background

CH is largely caused by thyroid gland dysgenesis, and there is lack of a standardized approach for diagnosis, follow-up, education, and genetic counseling of patients with CH.

Patients and methods

Genetic counseling and thyroid ultrasonography (US) were done. Blood samples were collected from 56 children (30 girls and 26 boys) with CH, diagnosed on the basis of neonatal screening program done by Egyptian Ministry of Health and Population, Central Health Laboratories, Hormones and Tumour Marker Department. All patients confirmed biochemically with low free thyroxine and high thyroid-stimulating hormone levels were enrolled as cases (group I), along with 56 apparently healthy individuals as controls (group II), who attended the Genetic laboratory of Genetic and Endocrinology Unit, Paediatric Department, Faculty of Medicine, Menoufia University, Egypt.

Results

A total of 16 (28.6%) patients had poor response to treatment. They were on a high dose of L-thyroxin (100 µg/day or more), with their US findings ranging from normal thyroid sonar in six patients, hypoplastic gland in four patients, and thyroid agenesis in six patients. All healthy control children showed normal US findings.

Conclusion

US is the first-choice imaging method in revealing the etiology of CH. Family counseling is a key component for enhancing the care of patients with CH.

Keywords:

congenital hypothyroidism, family counseling, ultrasound

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Introduction

Congenital hypothyroidism (CH) has been considered as one of the commonest preventable endocrinal disorders causing mental retardation all over the world, with a frequency of one in every 3000–4000 newly born births. Most of the neonates with CH appeared normal with no detectable findings, and in the absence of effective screening, treatment may be delayed [1].

Clinical follow-up of these children is critical to ensure that they receive appropriate monitoring and management. The American Academy of Paediatrics and the European Society For Paediatric Endocrinology have published guidelines for the treatment of CH cases which recommended follow-up until at least 3 years of age [2].

Family counseling is a key component to enhance the care of a patient with CH.

Ultrasound (US) is a good, safe, and primary tool for diagnosis and for guiding treatment, doses, and

prognosis. It decreases radiation exposure and cost, and is mainly helpful in assessing thyroid volume [3].

Overall, 85% of affected cases are due to thyroid dysgenesis. Apart from thyroid developmental defect, dyshormonogenesis accounts only for 15% of cases [4].

Our aim was to search for the risk factors of cases with poor controlled CH in correspondence to their clinical aspect.

Patients and methods

The present study was conducted on 56 children with CH, including 30 girls and 26 boys. Their mean ages were 4.6 ± 4.2 years (group I). They were recruited

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from attendants of Genetic and Endocrinology Unit, Paediatric Department, Faculty of Medicine, Menoufia University, during the period from June 2016 to March 2018. Cases with transient CH, of known etiology owing to maternal thyroid disorder, maternal intake of antithyroid drugs, and premature delivery were excluded. Moreover, 56 apparently healthy age-matched and sex-matched children (29 girls and 27 boys, with mean ages of 5.2 ± 2.7 years) were taken as controls (group II). Informed written consent was taken from the participants and their parents, after approval of the study by Menoufia University Ethics Committee under the guidance of Helsinki Declaration. Diagnosis of CH was based on the reference levels of Central Egyptian Health Laboratories during neonatal screening program, with low thyroxine (T4) levels (reference range, 10.30–28.30 pmol/l) and high thyroid-stimulating hormone (TSH) levels (reference range, 0.70–5.70 mU/ml). Complete thyroid profile by enzyme-linked immunosorbent assay technique was done for confirmation of abnormal screening results. Clinical data evaluation included complete history, family pedigree construction, and clinical examination applied. Data about gestational age, perinatal events, and infant's birth weight, in addition to family history of similar conditions, were collected from the patient's medical records plus monitoring regimens of L-thyroxine therapy [2]. Intelligence quotient was assessed by appropriate age-dependent methods. Thyroid scanning is a good and safe measure. Thyroid scanning is performed in supine position, with the neck hyperextended, using Philips US device (Philips health care, Andover, MA, US), model HD11XE, for evaluation of the presence or absence of thyroid gland in its anatomical location, detailed views about its texture, and other structural abnormalities. Family counseling is a program that consists of providing information and professional guidance to members of a family concerning specific health matters [5]. It consists of face-to-face discussion, in two visits or more. The first visit included the explanation of how the diagnosis made, the line of treatment, follow-up, their importance, and thyroid US done. The second visit included informing the families about the results of investigations, strict follow-up of doses aiming to keep the free T4 concentration at the upper end of the normal range, and TSH suppressed into the normal range; identifying the causes of patient's poor response such as parent's noncompliance; and discontinuation of treatment especially in patients with thyroid dysgenesis. The subsequent visits showed the regimen of follow-up, which should occur at 2 weeks, 6 weeks, 3 months, then 2 monthly during the first year, and thereafter, at 3-month intervals until 3 years. There was discussion with the parents

regarding different obstacles about discontinuation of treatment at 3 years, especially if there is thyroid dysgenesis.

Statistical analysis

Student *t* test was used for comparing quantitative variables with independent parametric data, expressed as percentage, mean, and SD, whereas Fisher's exact test or χ^2 test was applied for qualitative analysis through SPSS (Released 2011, IBM SPSS Statistics for windows version 20.0.; IBM Corp., Armonk, New York, USA).

Statistical significance was set as follows: nonsignificant at *P* value more than 0.05, significant at *P* value less than or equal to 0.05, and highly significant at *P* value less than or equal to 0.001.

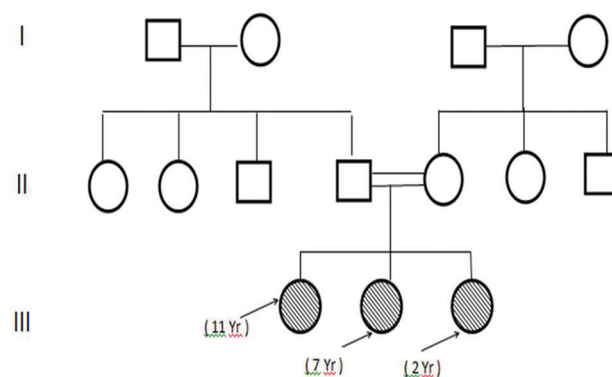
Results

Demographic and clinical characteristics of the whole participants are shown in Table 1. Among the 56 patients, the antenatal history showed that 22 (39.3%) patients had a history of parental consanguineous marriage, whereas 34 (60.7%) patients had a history of nonconsanguineous marriage. There were three (5.4%) female siblings of consanguineous marriage who had CH (Fig. 1).

Items suggestive for CH were in the form of jaundice, excessive sleep, decreased activity, hoarse cry, and delayed stooling, which were in the percentage of 60.7, 28.6, 12.4, 7.1, and 7.1%, respectively; maternal hyperthyroidism was a risk factor and predictor of CH (Table 2).

No significant difference was noticed between patients and control regarding BMI.

Figure 1



Three-generational pedigree analysis. Pedigree of a family having three affected female siblings with CH. CH, congenital hypothyroidism.

Table 1 Characteristic data of the studied groups

Sociodemographic characteristics	Cases (n=56)	Controls (n=56)	Test of significance	P
Age (years)			U=1.9	0.06 NS
Mean±SD	4.6±4.2	5.2±2.7		
Median				
Sex [n (%)]				
Male	26 (46.4)	27 (48.2)	$\chi^2=0.03$	0.85 NS
Female	30 (53.6)	29 (51.8)		
Consanguinity [n (%)]			$\chi^2=0.00$	1.00 NS
Positive	22 (39.3)	22 (39.3)		
BMI (mean±SD)	17.8±4.1	18.7±4.6	t=1.08	0.28 NS
Thyroid US [n (%)]			Fisher's exact test=33.8	≤0.001 HS
Both thyroid lobe and isthmus are average in size	36 (64.3)	56 (100)		
No detectable thyroid tissue	10 (17.8)	0 (0)		
Small-sized right lobe with nonvisualized isthmus and left lobe	4 (7.1)	0 (0)		
Agenesis of right-thyroid lobe with slightly hypovascular left lobe	4 (7.1)	0 (0)		
Both thyroid lobes are seen echogenic, homogenous and isthmus not seen	2 (3.5)	0 (0)		
Neonatal jaundice [n (%)]			$\chi^2=38.7$	≤0.001 HS
Positive	34 (60.7)	3 (5.4)		
Response to treatment [n (%)]			10.6	≤0.01 HS
On ordinary dosage	40 (71.4)	0 (0)		
On high dosage	16 (28.6)	0 (0)		
TSH (mU/ml) (mean±SD)	27.04±56.3	4.11±0.86	U=7.8	≤0.001 HS
T4 (pmol/l) (mean±SD)	11.05±9.1	19.2±3.2	U 4.40	≤0.001 HS
Degree of mentality [n (%)]			Fisher's exact test=10.8	≤0.001 HS
Normal	46 (82.1)	65 (100)		
Mild MR	2 (3.6)	0 (0)		
Border line MR	4 (7.1)	0 (0)		
Moderate MR	4 (7.1)	0 (0)		

HS, highly significant; MR, mental retardation; T4, free thyroxine; TSH, thyroid-stimulating hormone; US, ultrasonography. P: nonsignificant ($P>0.05$).

Table 2 Multivariate logistic regression analysis for risk factors predictor for congenital hypothyroidism

Variables	Wald	Significance	B (OR)	95% confidence interval	
				Lower bound	Upper bound
Sex	0.038	0.84	1.07	0.50	2.32
Consanguinity	0.73	0.30	0.67	0.26	1.66
Maternal hyperthyroidism	4.12	0.04	5.8	1.06	31.70
Birth weight	0.22	0.96	0.97	0.28	3.36
Decrease activity	0.001	0.99	0.001	0.00	0.00
Hoarse cry	0.001	0.99	0.001	0.00	0.00
Jaundice	1.09	0.29	0.17	0.007	4.52
Increase sleep	0.00	0.99	0.001	0.00	0.00
Hospitalization	0.001	0.99	0.001	0.00	0.00
TSH	10.4	0.001	0.199	0.075	5.30
T4	9.51	0.002	1.56	1.17	2.08
Thyroid agenesis	3.76	0.05	0.66	0.03	2.35

OR, odds ratio; T4, free thyroxine; TSH, thyroid-stimulating hormone.

Our study reported that there was a significant difference in mentality between patients and control groups ($P \leq 0.001$). Parental noncompliance and discontinuation of treatment for nonreasonable causes and thyroid dysgenesis were the main causes of this significant difference. Overall, four (7.1%) patients had moderate mental retardation (two patients of them had thyroid agenesis), two (3.6%) patients had mild mental retardation (skipped the neonatal screening programs), and four (7.1%) patients had borderline mental

retardation (patients were not regular on treatment, and two patients of them had thyroid hypoplasia).

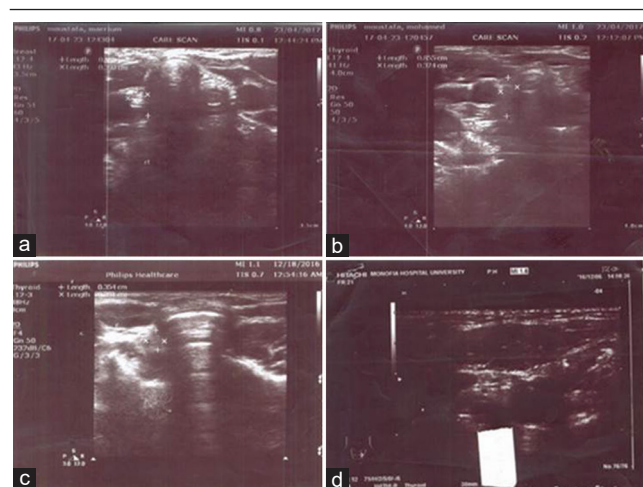
US findings showed that 36 (64.3%) patients with CH (both thyroid lobes and isthmus are average in size) corresponding to dysmorphogenesis and 10 (17.9%) patients had nondetectable thyroid tissue, and also four (7.1%) patients had small-sized right lobe with nonvisualized isthmus and left lobe. In addition, four (7.1%) patients had agenesis of

right-thyroid lobe with slightly hypovascular left lobe, and two (3.5%) patients had both thyroid lobes seen echogenic, homogenous echo pattern, and isthmus not seen (Fig. 2).

Regarding biochemical analysis, our results indicated a highly significant value for average levels of TSH and T4 (27.04 ± 56.3 and 11.05 ± 9.1 , respectively) for cases in comparison with controls values (4.11 ± 0.86 and 19.2 ± 3.2 , respectively); markedly elevated TSH and decreased T4 are predictors of thyroid dysgenesis (Table 3).

A total of 16 (28.6%) patients had poor response to treatment. They were on a high dose of L-thyroxine (100 µg/day), and their US findings ranged from normal thyroid sonar (six patients), hypoplastic gland in four patients, and thyroid agenesis in six patients. All healthy control children showed normal US findings.

Figure 2



Thyroid ultrasound of selected four different thyroid states: (a) thyroid hypoplasia (isthmus not seen), (b) normal thyroid gland, (c) thyroid hypoplasia (small-sized right-thyroid lobe with nonvisualized isthmus and left thyroid lobe), and (d) thyroid agenesis (nonvisualized thyroid gland).

Family counseling was done for all patients (Table 4).

Discussion

Family counseling is a key component to enhance the care of patients with CH.

This is a retrospective study conducted on patients with CH. Demographic criteria of this study patients revealed that among the 56 children with CH, 30 (53.6%) were females and 26 (46.1%) were males, with a female predominance.

Similarly, Supakul *et al.* [6] showed female sex frequency in CH and identified that among 124 total number of cases, 71.7% were girls, whereas 28.3% were boys.

In our study, 22 (39.3%) patients had a history of parental consanguineous marriage and 34 (60.7%) patients had a history of nonconsanguineous marriage. We reported three female siblings of parental consanguineous marriage who had CH. Similarly, Sindhuja *et al.* [7] showed that CH is usually sporadic, but up to 5% of thyroid dysgenesis is familial, and CH caused by organification defects is often recessively inherited. More recently, there is growing evidence for the role of gene defects causing CH associated with thyroid dysgenesis.

Clinical findings suggestive for CH were in the form of jaundice, excessive sleep, decreased activity, hoarse cry, and delayed stooling, which were in the percentages of 60.7, 28.6, 12.4, 7.1, and 7.1%, respectively.

The results of this study showed that clinical manifestations were absent in a high percentage of patients. However, in those who presented with positive clinical criteria, high percentage had only one or two symptoms, and low percentage of patients had more than two symptoms, which correlates with another study Buyukgbiz [8], which revealed that most

Table 3 Multivariate logistic regression analysis for risk factors predictor for thyroid dysgenesis

Variables	Wald	Significance	B (OR)	95% confidence interval	
				Lower bound	Upper bound
Sex	0.05	0.81	1.17	0.30	4.4
Consanguinity	0.25	0.61	1.47	0.32	6.72
Maternal hyperthyroidism	0.001	0.99	0.98	0.00	0.00
Birth weight	0.36	0.54	0.50	0.05	4.74
Decrease activity	7.37	0.007	0.09	0.01	0.52
Hoarse cry	0.042	0.83	1.27	0.12	12.9
Jaundice	1.11	0.29	0.47	0.122	1.88
Increase sleep	3.56	0.05	0.26	0.06	1.05
Hospitalization	0.26	0.60	0.67	0.15	2.98
TSH	9.82	0.002	0.903	0.84	0.962
T4	0.63	0.424	0.966	0.88	1.05

OR, odds ratio; T4, free thyroxine; TSH, thyroid-stimulating hormone.

Table 4 Family counseling results of the studied patients

Obstacles	Results
Parent's noncompliance and discontinuation of treatment for nonreasonable causes	The parents are now orientated about the extreme importance of L-thyroxin therapy
Parents were not aware about the value of doing thyroid US to their children	US done to all children; there were 10 children with agenesis, 10 with hypoplasia, and 32 with normal thyroid gland (dysmorphogenesis)
Poor response to treatment with high levels of TSH and low levels of T4, especially if there is thyroid dysgenesis	The parents are now orientated about the main cause of poor response to treatment, which is thyroid dysgenesis, and the importance of regular follow-up to adjust the dose according to TSH and T4 levels
Parents were worried about discontinuation of treatment after three years of age	Every parent became aware, whether he/she will be given a trial of treatment or not
	Patients with dysgenesis should not stop the treatment

T4, free thyroxine; TSH, thyroid-stimulating hormone; US, ultrasonography.

neonates born with CH had normal appearance and no detectable physical signs.

These results highlight the otherwise favorable outcome on mentality state owing to the preferential upgraded assistance of the Egyptian Ministry of Health and Population in constructing the Central New Born Screening Laboratory to stand as of the largest screening facilities, based on the number of heel-prick tests for CH conducted per year [9,10].

In our sample, we reported parental noncompliance, and eight children were lost to follow-up. Furthermore, we had two patients who skipped the neonatal screening programs. These patients showed developmental delay and mental retardation. These results are in concordance with Korzeniewski *et al.* [11], who reported some children with CH discontinued thyroid hormone replacement without appropriate medical advice and were lost to follow-up owing to parental noncompliance, which is a significant issue in children managed for CH.

Our results correlate also with Kurian and Jungbluth [12] who reported, normal thyroid metabolism is essential for human development, including the formation and functioning of the central and peripheral nervous system. Our findings also were in concordance with Grosse and Van Vliet [13], who showed ~28% of children with CH have intellectual disability. The mean intelligence quotient has shown an increase by 10–20 points in patients with CH before and after introduction of screening programs in these countries.

Our results and the other literature reviews illustrate the extreme importance of family counseling. Family education consists of face-to-face discussion, as well as paper and electronic resources provided to the family. This includes medical education highlighting the extreme importance of levothyroxine therapy, laboratory monitoring, and clinical follow-up [14].

Regarding our US findings, among a total number of 56 patients, there were 36 (64.2%) patients diagnosed

as dysmorphogenesis (normal thyroid gland), whereas there were 10 patients diagnosed as hypoplastic gland and 10 diagnosed as thyroid agenesis. In total, thyroid dysgenesis was seen in 35.8%. Our result do not correlate with those of Rastogi and LaFranchi [4], in which thyroid dysgenesis accounted for 85% of permanent, primary CH, whereas inborn errors of thyroid hormone biosynthesis (dysmorphogenesis) accounted for 10–15% of cases.

Of 56 patients, there were 16 (28.6%) patients who were controlled poorly on treatment, and they were on high dosage of L-thyroxin (100 µg/day). Their US findings ranged from normal thyroid sonar to hypoplastic and aplastic gland. There were three affected female siblings of consanguineous marriage who had CH. The oldest one was 11 years old, and her laboratory results were free thyroxine (FT4) of 1.4 ng/dl and TSH of 13.5 mIU/ml. The second girl was 7 years old, and her laboratory results were FT4 of 1.71 ng/dl and TSH of 17.4 mIU/ml. The third girl was 2 years of age and her laboratory results were FT4 of 1.69 ng/dl and TSH of 20.4 mIU/ml. The three girls had a poor response to treatment and were on a high dose of L-thyroxin (100 µg/day). Their US findings of thyroid gland were normal in size and shape (dysmorphogenesis). Our results correlated with Rastogi and LaFranchi [15], in which, thyroid dysmorphogenesis accounted for 10–15% of CH cases. Thyroid agenesis is a main risk factor for poorly controlled patients. Our results reported there were six patients with thyroid agenesis who were poorly controlled on the treatment. One of them was an 11-year-old girl, with thyroid agenesis, and her laboratory results were FT4 of 0.93 ng/dl and TSH of 309 mIU/ml. She was on high dose of L-thyroxin (300 µg/day). This case strongly supports that thyroid agenesis is a main risk factor for poor control of the disease. Moreover, four children with thyroid hypoplasia are on high dosage of L-thyroxin, and these results are in concordance with Castanet *et al.* [16]. Moreover, four children with thyroid hypoplasia are on high dosage of L-thyroxin. Similarly, Ordookhani *et al.* [17] showed that thyroid hypoplasia represent 5% of thyroid dysgenesis.

In our study, the parents are now orientated about the value of imaging studies, and thus, the main cause of poor response to treatment, that is, thyroid dysgenesis, and the importance of regular follow-up to adjust the dose according to TSH and T4 levels, in line with The American Academy of Pediatrics and the European Society For Pediatric Endocrinology, which published guidelines for the treatment of CH cases which recommended follow-up until at least 3 years of age [2].

Conclusion and recommendation

The etiology of CH should clearly be defined at diagnosis. So US is mandatory in diagnosing and guiding treatment, doses and prognosis and should be done for all patients of CH at the first visit.

The development of consistent best practice and educational guidelines, as well as readily available resources should be adopted at the regional and national levels.

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Conflicts of interest

There are no conflicts of interest.

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