Original Article

Etiology of congenital hypothyroidism in Isfahan: Does it different?

Mahin Hashemipour[1,2,3], Mahmoud Ghasemi[1], Silva Hovsepian[3], Kamal Heiydari[4], Ali Sajadi[4], Rezvaneh Hadian[4], Marjan Mansourian[5], Naghme Mirshahzadeh[2], Roya Kelishadi[3], Marzie Dalvi[4]

[1]Department of Pediatrics, [2]Isfahan Endocrine and Metabolism Research Center,[3] Child Growth and Development Research Center, [4]Isfahan Health Center, [5]Department of Biostatistics and Epidemiology, Health School, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Considering the higher prevalence of congenital hypothyroidism (CH) in Iran and the importance of determination of the etiology of CH for assessing appropriate treatment strategies, understanding the pathogenesis of CH and the implications of its inheritance and prognosis, the aim of this study was to determine the etiology of CH 7 years after initiation of the program in Isfahan province.

Materials and Methods: In this cross-sectional study, children with a primary diagnosis of CH studied. They clinically examined and their medical files were reviewed by a Pediatric Endocrinologist. Considering screening and follow-up lab data and radiologic findings the etiology of CH was determined. Screening properties of different etiologies of CH was compared.

Results: In this study, 437 patients with permanent CH (PCH) were studied. Etiology of PCH in 316 (72.3%) and 121 (27.7%) of cases was thyroid dyshormonogenesis and thyroid dysgenesis, respectively. Prevalence of agenesis, ectopia, hypoplasia and hemiagenesis in thyroid dysgenetic patients was 13.3%, 6.4%, 4.3% and 3.7% respectively. Mean of thyroid stimulating hormone in screening, recall and after discontinuing treatment at 3 years of age was significantly lower in dyshormonogenetic CH patients than dysgenetic ones($P < 0.01$).

Conclusion: Seven years of our experiences in CH screening program indicated that the etiology of CH in Isfahan, with a higher rate of CH, with a predominance of thyroid dyshormonogenesis is different from most of the studies world-wide and similar to other reports from Iran. The findings of the current study provide us baseline information for determination of CH pathogenesis in this region.

Key Words: Congenital hypothyroidism, dysgenesis, dyshormonogenesis, permanent

Address for correspondence:
Dr. Silva Hovsepian, PhD candidate, Child Growth and Development Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: silvahovsep@hotmail.com
Received: 01.07.2013, **Accepted:** 09.09.2013

Access this article online	
Quick Response Code:	Website: www.advbiores.net
	DOI: 10.4103/2277-9175.124658

INTRODUCTION

Congenital hypothyroidism (CH) is defined as thyroid hormone deficiency present at birth. CH considered as the most common endocrine disorder and causes of preventable mental retardation in children with a prevalence rate of 1 in 2000-4000 live birth.[1,2]

CH may result from defects in the proteins involved in thyroid hormone synthesis known as thyroid

How to cite this article: Hashemipour M, Ghasemi M, Hovsepian S, Heiydari K, Sajadi A, Hadian R, *et al.* Etiology of congenital hypothyroidism in Isfahan: Does it different?. Adv Biomed Res 2014;3:21.

dyshormonogenesis or defects in the development of the thyroid gland known as thyroid dysgenesis.[3] Several studies world-wide indicated that the most common cause of CH in 85% of cases is thyroid dygsenesis and in reminder 15% is thyroid dyshormonogenesis.[4]

Establishing of CH screening since 1970 and its development have provided us the opportunity for early detection and treatment of CH and preventing its related neuoro developmental consequences.[5,6] In addition, it provides essential epidemiological and etiological information, which could be helpful in appropriate management of CH.[6]

Although some clinicians believe that determination of the etiology of CH is not obligatory due to that the management of CH is similar in its different etiologies, but others believe that it is as important as diagnosis and treatment of CH.[7] However, many studies indicated that required dose of L-thyroxine is different in those CH patients with thyroid agenesis than those with ectopic thyroid gland, hypoplasia or thyroid dyshormonogenesis, because neuropsychological development is worse than other mentioned etiologies.[8] Hence, determining the etiology of CH is an important issue in CH screening program of each country for predicting severity of the disorder, its outcome and proper treatment and L-thyroxine titration. Also, it is crucial for understanding the pathogenesis of the disorder and providing reliable parental genetic counseling.

Reports before and after nationwide CH screening program in Iran have demonstrated that the prevalence of CH is higher in Iran than other regions.[9-11] In addition, some studies indicated that the etiology of CH in Iran, with a higher rate of thyroid dyshormonogenesis, is not similar to that reported previously world-wide.[12-14]

Thus, considering the higher prevalence of CH in Iran and the importance of determination of the etiology of CH for assessing appropriate treatment strategies, understanding the pathogenesis of CH and implications of its inheritance and prognosis, the aim of this study was to determine the etiology of CH 7 years after initiation of the program in Isfahan province.

MATERIALS AND METHODS

In this cross-sectional study, children with permanent CH (PCH) diagnosed at 3 years of age referred to Isfahan Endocrine and Metabolism Research Center and all health centers in Isfahan province for treatment and follow-up from March 2002 until September 2009 during CH screening in Isfahan were enrolled.

The Medical Ethics Committee of Isfahan University of Medical Sciences approved the study protocol.

All children with PCH were recalled. They clinically examined and their medical files were reviewed by a pediatric endocrinologist. The etiology of CH in patients with PCH was determined according to their radiologic reports (ultrasonography and/or scintigraphy report) and laboratory and clinical examination results. Those who had not radiologic information referred for radiologic study. The radiologic study, which recommended at 3 years of age was ultrasonography. PCH patients were classified as those with dyhormonogenetic PCH and those with disgenetic PCH and different etiologies of thyroid disgenesia including agenesia, hemiagenesia, ectopia and hypoplasia. The screening properties of PCH patients with different etiology of CH compared with each other.

CH screening in Isfahan

From May 2002 until April 2005, T4 and *thyroid stimulating hormone (*TSH) serum concentrations of all 3-7 day old newborns were measured by radioimmunoassay and immunoradiometric assay, respectively, using Kavoshyar (Iran-Tehran) kits. Thyroid function tests were performed by Berthold-LB2111 unit gamma counter equipment using serum samples. In this period neonates with TSH > 20 were recalled.

After implementation of nationwide CH screening program in Iran in April 2005, screening was performed using filter paper. Neonates with TSH > 5 were recalled and those with abnormal T4 and TSH levels on their second measurements (TSH > 10 mIU/l and T4 < 6.5 μg/dl) were diagnosed as CH patient and received treatment and regular follow-up.

Levothyroxin was prescribed for hypothyroid neonates at a dose of 10-15 μg/kg/day as soon as the diagnosis was confirmed. Neonates with CH were followed-up according to the CH screening guideline for appropriate treatment regarding the level of TSH, T4, height, weight and other supplementary tests. In accordance with screening program, in order to provide a similar treatment and follow-up protocol, 2-3 workshops annually was held in different cities of the province.

Permanent and transient cases of CH were determined at the age of 3 years by measuring TSH and T4 concentrations 4 weeks after withdrawal of L-T4 therapy. Patients with normal TSH level (TSH < 10) considered as transient CH. Patients with elevated TSH levels (TSH > 10 mIU/l) and decreased T4 levels (T4 < 6.5 μg/dl) were considered as PCH sufferers. The etiology of CH was determined by thyroid scan and/or ultrasound before

treatment in the neonatal period or at the age of 3 years after confirming the permanency of CH.[14]

ETIOLOGY OF PCH

The etiology of CH was determined by thyroid scan and/or ultrasound before treatment in the neonatal period or at age 3 years after confirming the permanency of CH.

Thyroid scintigraphy was performed before or within the first 4 days of treatment initiation. The infants were fed just before thyroid scintigraphy to keep them quiet. Thyroid scintigraphy was performed using a gamma camera equipped with a pinhole collimator (Stintrone, Germany), 20 min after intravenous injection of 0.5-1 mci Tc99.

Thyroid ultrasonography has no time limitation and could be performed at any time during follow-up. The sonogram was evaluated for the following features: (1) Absence or presence of the thyroid gland in usual anatomical location, (2) absence or presence of the thyroid lobes and isthmus and (3) presence of thyroid in ectopic localization. Agenesis is characterized by a complete absence of thyroid tissue. Thyroid ectopia was defined as thyroid tissue localization other than in the lower part of the neck. The anterior cervical area was systematically studied for the presence of thyroglossal duct remnants from the foramen caecum to the normal anatomic position of the thyroid gland and even lower, above the sternal manubrium. Based on the ultrasonographic and scintigraphic studies, patients were classified into two main categories: (1) Normal gland in the usual location and (2) abnormal results, which contains agenesia and ectopia in the case of scintigraphy and agenesia, ectopia and hypoplasia in the case of ultrasonography.[15]

The etiology of CH among patients with PCH was determined as follows: thyroid dysgenesis cases (agenesis, hemiagenesis, ectopia and hypoplasia) were confirmed by both scintigraphic and ultrasonographic imaging and patients with abnormal thyroid function test results, but normal scintigraphy and ultrasonography were considered to be cases of dyshormonogenesis.

Final diagnosis was performed by a Pediatric Endocrinologist, according to the clinical, biochemical and radiology data in each CH patient.

Statistical analysis

Obtained data were analyzed using the SPSS (Release 20.0, SPSS Inc., Chicago, IL, USA) software and ANOVA, *T*-test.

RESULTS

In this study, 437 patients with PCH were studied. According to the clinical and paraclinical including both laboratory and radiologic findings, the etiology of PCH in 316 (72.3%) of cases was thyroid dyshormonogenesis. Thyroid dysgenesis was present in 121 (27.7%) of studied patients. Prevalence of agenesis, ectopia, hypoplasia and hemiagenesis in thyroid dysgenetic patients was 13.3%, 6.4%, 4.3% and 3.7% respectively.

Demographic and screening characteristics of studied population in dysgenetic and dyshormonogenetic patients with CH are presented in Table 1.

Demographic and screening characteristics of different etiologies of dysgenetic CH patients are presented in Table 2.

DISCUSSION

In this study, etiology of CH among patients diagnosed during 7 years of CH screening program in Isfahan was determined. The results indicated that thyroid dyshormonogenesis is the most common etiology of PCH in Isfahan and in patients with thyroid dyshormonogenesis both screening and recall TSH level are lower than other etiologies.

The prevalence of PCH in Isfahan after 7 years of CH screening initiation was reported to be 1 in 1133 live births (unpublished data). Many studies world-wide indicated that the most common cause of CH is thyroid dysgenesis and thyroid dyshormonogenesis is the cause of CH in 15% of patients with CH.[16,17] The results of the current study were not similar to the majority of the reports in this field. However, it was in line with other studies in Iran, Saudi Arabia and a study in the USA.[12-14,18,19]

Karamizadeh *et al*. in Shiraz-Iran, located in the central part of the country, indicated that the etiology of CH in 57% and 43% of cases were dyshormonogenesis and dysgenesis, respectively. Similar to our findings among patients with thyroid dysgenesis the most common cause was agenesis.[13]

In our previous study in Isfahan city, prevalence of thyroid dyshormonogenesis and dysgenesis was 58.8% and 42.2%, respectively.[14]

Ordookhani *et al*. found that 51.4% and 48.6% of patients had dysgenesis and dyshormonagenesis, respectively[12] and studies from Saudi Arabia[18] and the USA by Eugster *et al*.[19] also found that dyshormonogenesis was more prevalent.

Table 1: Demographic and screening characteristics of studied population in dysgenetic and dyshormonogenetic patients with CH

Variables	Dyhormonogenetic CH patients *n* = 316 (%)	Dysgenetic CH patients *n* = 121 (%)	*P* value
Weight (g)	3060.3±642.9	2949.0±638.5	0.862
Height (cm)	49.1±3.9	49.6±3.7	0.430
Head circumferences (cm)	34.9±1.5	35.4±1.9	0.367
Sex (female/male)	105/128 (0.8)	65/53 (1.2)	0.048
Maturity (term)	92.9	90.2	0.303
Type of delivery			
Normal	38.9	31.4	0.532
Caesarean	61.1	68.6	
Parental consanguinity			
First degree	23.3	21.2	0.357
Second degree	16.4	10.6	
History of thyroid disorders			
Mothers	14.8	9.9	0.521
Fathers	3.6	1.1	
Mean of screening TSH (mlu/L)	39.9±36.1	105.9±95.2	0.000
Mean of recall TSH (mlu/L)	45.1±44.8	98.8±81.9	0.000
Mean age at treatment initiation (days)	25.4±26.1	19.5±15.2	0.183
Mean of drug dose (μg/day)	97.4±23.2	98.8±19.6	0.333
Mean of TSH_before_treatment_discountinuing (mlu/L)	2.2±3.5	1.9±2.5	0.836
Mean of TSH_after_treatment_discountinuing (mlu/L)	33.7±54.3	50.5±42.1	0.010

CH: Congenital hypothyroidism; TSH: Thyroid stimulating hormone

Table 2: Demographic and screening characteristics of different etiologies of dysgenetic CH patients

Variables	CH patients with thyroid agenesia *n* = 58 (%)	CH patients with thyroid ectopia *n* = 28 (%)	CH patients with thyroid hypoplasia *n* = 19 (%)	CH patients with thyroid hemiagenesis *n* = 16 (%)	*P* value
Weight (g)	2949.0±638.5	3134.5±393.6	3228.2±357.3	2998±604.6	0.691
Height (cm)	49.6±3.8	49.7±2.8	45.0±16.9	49.4±3.7	0.155
Head circumferences (cm)	35.4±1.9	35.4±1.4	36.4±1.3	34.1±2.1	0.016
Sex (female/male)	1.4	1.25	1.7	0.4	0.130
Maturity (term)	85.4	94.7	100	88.9	0.385
Type of delivery					
Normal	18.2	33.3	44.4	60	0.706
Caesarean	81.8	66.7	55.6	40	
Parental consanguinity					
First degree	27.5	19.04	7.7	18.2	0.646
Second degree	12.5	9.5	15.4	0	
History of thyroid disorders					
Mothers	9.7	15.4	7.7	0	0.359
Fathers	0	0	0	8.3	0.80
Mean of screening TSH (mlu/L)	105.9±95.2	81.9±50.8	48.7±31.3	87.5±111.0	0.000
Mean of recall TSH (mlu/L)	98.8±81.9	105.0±105.2	50.2±40.2	55.9±39.5	0.000
Mean age at treatment initiation (days)	19.5±15.7	23.5±32.1	22.4±15.7	15.2±10.3	0.328
Mean of drug dose (μg/day)	98.5±22.1	98.5±18.9	98.4±19.2	97.6±18.5	0.760
Mean of TSH before treatment discountinuing (mlu/L)	1.9±2.5	1.1±1.6	2.1±2.9	1.0±0.9	0.668
TSH after treatment discountinuing (mlu/L)	50.5±42.1	88.5±75.4	45.8±36.2	46.8±46.4	0.010

CH: Congenital hypothyroidism; TSH: Thyroid stimulating hormone

Though parental consanguinity considered as one of the probable cause of the high rate of thyroid dyshormonogenesis as well as higher prevalence of CH in our region,[20] but the screening properties of patients with dyshormonogenesis and dysgenesis in the current study did not indicate such a relationship.

It is expected that the prevalence of parental consanguinity be higher in dyhshormonogentic CH patients than dysgenetic ones, considering that the mode of inheritance in this group of patients is autosomal recessive and in dysgenetic patients is sporadic.[21] Previous studies demonstrated that the genetic component was presented in 2% of dysgenetic patients,[21] it seems that due to unknown factors such as ethnic differences or high rate of parental consanguinity, genetic factors have more significant role in dysgenetic patients in our region.

Though the overall rate of parental consanguinity was higher in CH patients in Isfahan,[20] but it seems that parental consanguinity have a role in higher incidence rate of both thyroid dyshormonogenesis and dysgenesis. Our results in this study was similar to our previous pilot study.[14]

However the role other genetic, autoimmune and environmental factors in the pathogenesis of CH should be investigated in our future studies.

Screening properties of CH patients with thyroid dyshormonogenesis and dysgenesis indicated that mean of TSH during in screening, recall and after discontinuing treatment at 3 years of age was significantly lower in those with dyshormonogenesis than dysgenesis. In addition, mean of TSH at mentioned times were significantly higher in dysgenetic CH patients with thyroid agenesis and ectopia. The results were similar to some studies in this field.[22,14]

In one study in Isfahan, we reported that thyroid disease specially hypothyroidism in mothers was significantly higher in CH patients than healthy neonates.[23] In this study, the overall rate of thyroid disorders among parents of CH patients was not different in various etiologies of CH. It is recommended to obtain more conclusive results the role of different type of thyroid disorders in various etiologies of CH investigate separately.

Another usefulness of determining the etiology of CH is in proper treatment of CH patients with different etiologies. Hanukoglu *et al*. have investigated the relationship of etiology to treatment in congenital hypothyroidism and indicated that CH patients with thyroid agenesis received the highest dose of L-T4, and dyshormonogenetic group received the lowest dose.[24] In the current study dose of levothyroxine was not different between dyshormonogenesis and dysgenesis as well as different etiological subgroups of thyroid dysgenesis.

Regarding sex ratio, previous studies showed that the female to male ratio is higher in PCH and the proportion is higher in those with ageneis of the thyroid gland than those with thyroid dyhormonogenesis.[25] The ratio is reported to be 2.4:1 for thyroid dysgeneis and 1:1 for thyroid dyhormonogenesis).[26] However, it seems that sex ratio in CH patients is vary in different ethnic and race.[27] In the current study, the ratio was higher in dysgentic than dyshormonogenetic group (1.2 vs. 0.8). It was not different significantly in different subgroups of thyroid dysgenesis. Our findings were in accordance with other studies.[25-27]

CONCLUSION

Seven years of our experiences in CH screening program indicated that the etiology of CH in Isfahan, with a higher rate of CH, with a predominance of thyroid dyshormonogenesis is different than most of the studies world-wide and similar to other reports from Iran. The findings of the current study provide us baseline information for determination of CH pathogenesis in this region.

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Source of Support: Isfahan University of Medical Sciences, **Conflict of Interest:** None declared.

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