

Congenital Hypothyroidism: Etiology and Growth-Development Outcome

Setila Dalili¹, Seyed Mahmood Rezvani², Hossein Dalili³, Zahra Mohtasham Amiri⁴, Hamid Mohammadi⁵, Sahar Abrisham Kesh², Mohammad Hassan Novin², Abdolreza Medghalchi⁶, and Hajar Gholamnezhad²

¹ Pediatrics Growth Disorders Research Center, 17 Shahrivar Hospital, Faculty of Medicine, Guilan University of Medical Sciences, Guilan, Iran

² Health Center, Guilan University of Medical Sciences, Guilan, Iran

³ Department of Pediatrics, Breastfeeding Research Center, Tehran University of Medical Sciences, Tehran, Iran

⁴ Department of Social Medicine, Faculty of Medicine, Guilan University of Medical Sciences, Guilan, Iran

⁵ Department of Pediatrics, Faculty of Medicine, Shiraz University of Medical Sciences, Fars, Iran

⁶ Eye Research Center, Amiralmomenin Hospital, Faculty of Medicine, Guilan University of Medical Sciences, Guilan, Iran

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Abstract- One of the most preventable causes of mental and growth retardation is congenital hypothyroidism (CH). This study tries to investigate growth and mental outcome of patients with CH. Since November 2006 and November 2007 in Guilan province, north of Iran, all neonates who were diagnosed with CH, evaluated for etiology of CH by laboratory follow up, thyroid sonography or scan. Growth and development of patients with CH were compared with healthy children in same age, geographical area, social and economical classes in four years old. Demographic characteristics including height, weight, and head circumference at birth, follow up time (four years old) and IQ (Good enough test) were recorded in questionnaires. Among 28904 screened neonates, 37 patients with CH were diagnosed. Incidence of CH was 1:781 in live births, 20 (54%) in female neonates and 17 (46%) in male neonates. The incidences of permanent and transient hypothyroidism were 43.2% (16 cases) and 56.8% (21 cases) respectively. The incidence of permanent and transient hypothyroidism were 16 (43.2%) and 21 (56.8%), respectively. In permanent CH, 11 cases (68.2%) had dysmorphogenesis and 5 cases (31.2%) had thyroid dysgenesis. Significant statistical difference was only in family history of thyroid disease (34, 3% Positive family history in CH vs. 13.2% in control group, *P*-value 0.03). All other demographic characteristics and IQ had no statistical difference. Patients with CH diagnosed through neonatal screening and treated had normal growth as general population that indicates effective screening program and treatment in this area (3.2%).

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Introduction

Congenital hypothyroidism (CH) with prevalence of 1:3000 – 1:4000, is the most common preventable cause of mental retardation in children (1,2). Screening is the most acceptable route of CH diagnosis because of vague clinical presentation at birth (3). Several studies have shown a strong association between intelligence, early treatment and disease severity in patients with CH (4-6).

Different factors influence final intelligence quotient such as early treatment, adequate doses and early detection. Present study focuses on epidemiology of CH and its effect on development of patients (6-8).

Materials and Methods

Between November 2006 and November 2007 in Guilan province, all neonates who were diagnosed with CH, evaluated for etiology of this disease. Permanent CH was confirmed in those with elevated serum TSH during 6-12 months, levothyroxine therapy and/or confirmed thyroid dysgenesis by thyroid sonography or scan. To distinguish between permanent and transient CH in other cases, around third year of follow up, levothyroxine therapy discontinued for four weeks in CH cases. Patients reevaluated by serum TSH and T4 measurement. Thyroid sonography also was performed in all patients around this time. All patients with TSH levels >10 mU/L after four weeks of levothyroxine

Corresponding Author: A. Medghalchi

Eye Research Center, Amiralmomenin Hospital, Faculty of Medicine, Guilan University of Medical Sciences, Rasht, Iran
Tel: +98 131 3229902, Fax: +98 131 3226101, E-mail address: setiladalili1346@yahoo.com

discontinuation, were diagnosed as a permanent congenital hypothyroidism. Demographic characteristics including height, weight, and head circumference at birth and follow up time (four years old) were recorded in questionnaires. Child number and mom's height also was included in questionnaires.

Growth and development of these patients were compared with healthy children in same age, geographical area, social and economical classes in around four years old. Their IQs were evaluated using the "Good Enough" test.

SPSS version 19 software was used to analyze the results. T-test was used to compare the mean values of the two groups.

Results

During first year of study, 28,904 neonates were screened in Guilan province. Recall rate was 2.3% (665 neonates) that lead to detection of 37 patients with CH.

Incidence of CH was 1:781 of live birth with 54 % (20 cases) in female neonates and 46% (17 cases) in male neonates (Table 1). According to the scintigraphic and/or ultrasonographic findings, the incidence of permanent and transient hypothyroidism were 43.2 % (16 cases) and 56.8 % (21 cases) respectively. Among 21 patients with transient CH, 7 patients had elevated TSH level, and normal T4 ("isolated hyperthyrotropinemia").

All patients with transient CH had normal thyroid glands. In permanent CH, 11 cases (%.68.2) had dysmorphogenesis, 5 cases (%.31.2) had thyroid dysgenesis (3 cases of agenesis or hypoplasia and 2 case of ectopia). The mean TSH values of transient CH patients were significantly lower than patients with permanent CH (88.03 ± 38.22 versus 21.27 ± 14.25 with P .value <0.0001). One of patients with CH had sickle cell disease, and the one had inborn error of metabolism, probably isovaleric acidemia.

Characteristics of all neonates with or without CH are summarized in Tables 2 and 3.

Table 1. Sex distribution of CH

Sex	CH		Total (% of total CH)
	Permanent (% of total CH)	Transient (% of total CH)	
Female	9	11	20 (54%)
Male	7	10	17(46%)
Total	16 (43.2 %)	21 (56,8 %)	37 (100%)

Table 2. Distribution of different demographic characteristics among infants with and without CH

Variable	Group	Mean \pm SD	Statistical Difference (P value)
Birth height (cm)	case	49.15 \pm 2.7	NS* difference (0.461)
	control	49.57 \pm 2.50	
Birth weight (g)	case	3238.41 \pm 603.44	NS difference (0.506)
	control	3329.21 \pm 559.55	
Birth head circumference (cm)	case	35.57 \pm 3.66	NS difference (0.113)
	control	34.22 \pm 1.75	
Age at follow up (month)	case	44.58 \pm 5.94	NS difference (0.76)
	control	44.15 \pm 5.95	
Height at follow up (cm)	case	100 \pm 5.87	NS difference (0.06)
	control	102 \pm 4.3	
Weight at follow up (Kg)	case	16.9 \pm 3.27	NS difference (0.105)
	control	17.33 \pm 2.77	
Head circumference at follow up (cm)	case	49.69 \pm 2.59	NS difference (0.587)
	control	49.94 \pm 1.18	
Mom height (cm)	case	158.56 \pm 6.67	NS difference (0.203)
	control	154.24 \pm 19.33	
Mom weight (kg)	case	72.01 \pm 15.1	NS difference (0.753)
	control	73.59 \pm 23.94	
Child number	case	1.7 \pm 0.85	NS difference (0.241)
	control	1.51 \pm 0.85	
IQ (good enough)	case	114.29 \pm 16.27	NS difference (0.936)
	control	114.38 \pm 20.61	

*NS: Non significant

Significant statistical difference was only in family history of thyroid disease; that was more common in CH. Positive family history in neonates with CH were 34.3% vs 13.2% in neonates without CH, *P*.value 0.03).

Although mean height in neonates with CH were more than neonates without CH (100 ± 5.87 vs 102 ± 4.3 , *P*.value 0.06), but there was no significant difference between these two groups.

Table 3. Comparison of different factors in case and control groups (with or without CH)

Factor		Case		Control		Comparison of distribution between case and control
		Number	Percent	Number	Percent	
Gender	Male	17	47.2%	18	47.4%	NS*
	Female	19	52.8%	20	52.6%	
Gestational Age	Preterm	2	5.6%	0	0%	NS
	Term	34	94.4%	37	100%	
	Postdate	0	0%	0	0%	
Birth weight	LBW-VLBW	5	13.9%	2	5.3%	NS
	Normal BW	27	75%	31	81.6%	
	LGA	4	11.1%	5	13.1%	
Delivery Route	C/S	24	66.7%	28	75.7%	NS
	NVD	12	33.3%	9	24.3%	
Parent consanguinity	Near	4	11.1%	4	10.5%	NS
	Far	1	2.8%	0	0%	
	None	31	86.1%	34	89.5%	
Family history thyroid disease	Yes	12	34.3%	5	13.2%	0.03
	No	23	65.7%	33	86.8%	

*NS: Non significant

Discussion

CH is the most frequent endocrine disorder in neonates. Controversy exists regarding the incidence of disease in different countries (1:1991 in Taiwan 1:1300 in the Netherlands or 1:1800 in Thailand and Lebanon (4,5,8-10). Most of studies in Iran also show higher incidence between 1:357 in Isfahan province by Hashemipour *et al.*, (11) up to 1:1465 in Fars province by karamyzade *et al.*, (12). This study with incidence of 1:781 is comparable to other Iranian studies, and it has significant higher incidence than most of reports from other countries. Regarding higher incidence in multiple Iranian studies, genetic predisposition of Iranian population is a probable cause, but significant variation of CH incidence in different areas of Iran has highlighted effects of environmental factors.

Shapira *et al.*, reported that standardization of the diagnostic criteria to classify permanent CH versus transient hypothyroidism is one of the major factors that change CH incidence. They concluded that this lead to increasing CH incidence in these last years (13).

These findings are reasonable clue to recommend initial focus on world standardization of the diagnostic criteria of CH. Considering high incidence of transient hypothyroidism in the present study and most of the other reports from Iran, this recommendation is more important in Iran.

Although the female/male ratio in this study was 1.17:1 but this is lower than most of reports in other countries, female to male ratio is around 2:1, and is comparable with other studies from Iran, Karamizadeh *et al.* related this difference to different etiologies of CH in Iranian populations (12).

In this study among 37 patients with CH, 43.2% (16 cases) and 56.8% (21cases) were confirmed to have the permanent and transient form of the disorder, respectively. This finding is although similar to that of other investigations in Iran such as Hashemipour *et al.* that reported incidence of permanent and transient CH 59.8% and 40.2% respectively. Karamizadeh *et al.*, published incidence of permanent and transient CH 53.6% and 46.4% respectively (11,12). But in this study incidence of transient CH is slightly more than permanent CH. Higher incidence of transient CH is similar to Gaudino *et al.*, and others reports (14-16). To find an interpretation for this difference, we reviewed causes of transient CH such as iodine deficiency in our population. Guilan province is a non-IDD area and, on the other hand, considering urine iodine level in school-aged children, Guilan province is at risk for iodine induced hyperthyroidism within 5-10 yrs of introducing iodized salt (17). So this can't be a cause of this change. Another point is that patients with high TSH and normal T4 labeled as transient hypothyroidism that had discontinuation of treatment in unusual time. Muge

Tamam *et al.*, reported 17% of 182 patients as “Isolated Hyperthyrotropinemia,” which were neither transient nor permanent cases of CH (3). They recommend these patients can be followed without hormone therapy.

This study showed similar results as previous investigation in Iran by Karamizadeh *et al.*, (12). There are same laboratory features in 23% of transient cases. These cases were labeled as transient hypothyroidism. We believe that this is a major factor for a higher rate of transient CH in Iran. These findings are reasonable to be recommended as initial focus for world standardization as the diagnostic and treatment criteria of CH.

In most articles and reviews, dysgenesis of thyroid gland is the most common cause of CH and dyshormonogenesis being the next one, but our results differ and show %68.2 dyshormonogenesis and %31.2 dysgenesis as causes of permanent CH. Interestingly thyroid agenesis also was more prevalent than thyroid ectopia among patients with thyroid dysgenesis. This result was consistent with other studies of Iranian populations. Hashemipour *et al.*, from Isfahan- Iran, also reported 58.8% and 42.2% as prevalence of dyshormonogenesis and dysgenesis, respectively and higher rate of agenesis than ectopia (11). Some similar results in other countries are also reported, such as the study of Eugster *et al.*, that indicated that dyshormonogenesis was more prevalent (57.1% of permanent CH) (15). It seems that different etiology of CH in Iran could lead to different pattern of permanent CH.

Between two groups of patients and control no statistical differences were in sex, weight, height, birth height, birth weight, birth circumference, mom height and weight, gestational age and IQs. Although, Dalili *et al.*, reported that low birth weight, postdate delivery and macrosomia were risk factors for CH, but this differences were probably because of low sample size (18). Same IQ in two groups, if indicates effective screening program and effective treatment for these patients in Guilan province, north of Iran.

Although mean height in healthy children is higher than children with CH, but no significant difference was between mean height in case and control groups (P -value= 0.06). These results were in accordance with the results of Grant *et al.*'s in London which indicated that by the age of 3-4 years, stature becomes normal in children with early treated CH (19). Feizi *et al.*, believed that CH patients had impaired growth development that was improved during follow up, but the catch-up time was earlier for head circumference and later for weight (20).

Patients with CH detected by neonatal screening had normal growth in general, suggesting that neonatal screening system of CH is performed efficiently from

detection to treatment of the disease in Iran.

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