Congenital Hypothyroidism: A Review of the Risk Factors

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Abstract- This study was aimed to evaluate the situation of congenital hypothyroidism (CH) in Guilan using the screening program and determine the correlation of CH with birth weight, gestational age and seasonality. During 2006 to 2010, in Guilan province, neonatal screening for CH by measurement of serum TSH level was performed in 3-5 days after birth. All neonates with TSH level ≥ 5mu/l were referred to endocrinologists and serum TSH, T3 and T4 were measured. Based on public health data and profiles, total number of newborns, gestational age, route of delivery, birth season and birth weight in all screened neonates was reviewed and for ones with CH, their TSH measurements was also recorded. During 5 years, 119701 neonates were screened and CH was confirmed in 10.8% (221) of the referral cases (prevalence=1:542). No significant statistical difference was seen between gender and birth season among patients with CH and the rest of the population. Interestingly, low birth weight (LBW) (31% vs. 4.9%, $P<0.01$), postdate delivery (1.4% vs. 0.2%, $P<0.01$) and macrosomia were more prevalent in CH versus normal population (Odds ratio for post-date delivery was 6.9 and for LBW was 3.2). Rate of normal vaginal delivery (NVD) was significantly higher in neonates with CH compared to normal population (39.2% vs. 29.2%, $P=0.01$). LBW, postdate delivery and macrosomia are risk factors for CH. No association between sex, birth season or caesarian section delivery was seen.

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Keywords: Congenital hypothyroidism; Low birth weight; Macrosomia; Postdate delivery

Introduction

Congenital hypothyroidism (CH) is the most common preventable cause of mental retardation in children (1). Lack of diagnostic clinical features at birth highlights the need of systemic screening methods to early diagnosis (2,3). Congenital hypothyroidism has a prevalence of 1:3000-1:4000 in newborns with increasing prevalence in more recent studies (4). Its rate varies depending on race, ethnicity and method of screening (5). It is believed that many other risk factors might influence the prevalence of CH (9,14-16). Confirming the cause and effect relationship between these risk factors and CH and identifying them might be helpful even in decreasing the incidence of CH. More practically, it can help to have a higher index of suspicion for CH in neonates with the identified risk factors. The aim of this study was to evaluate the incidence of CH in Guilan screening program and also to determine the correlation of congenital hypothyroidism with some of the factors that are highly spoken of as risk factors for CH such as: birth weight, gestational age and seasonality.

Materials and Methods

In Guilan province (one of Northern provinces of Iran), screening for CH is performed by TSH measurement on a filter paper blood spot and sampling was carried out between 3-5 days after birth which has been introduced since 2006. The screening program includes all hospital newborns in the Guilan province that are obligatorily referred to the health care center for their newborn screening for the three common and important congenital disorders namely CH, G6PD deficiency and phenylketonuria. Health care providers take the heel

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stick sample for serum TSH level and each parent is responsible for following their child's screening results in order to be able to have a written permission to get their child's birth certificate.

This study was performed retrospectively based on the available data of this screening program in the public health center including the number of newborns, gestational age, route of delivery, birth season and birth weight in Guilan province, carried out during 2006 to 2010. No extra intervention was performed for these neonates and therefore there was no ethical issue in the data gathering. Based on the screening protocol, all newborns with a baseline TSH level ≥ 5mu/l, by filter paper assay, as in the practice in all parts of Iran, have been referred to an endocrinologist to confirm the results by checking a serum TSH, T4 and T3. Serum TSH was measured by immunoradiometric assay (Xit immunotech, Belgium).

Newborns clinically suspicious of having sepsis or those who had respiratory distress syndrome or were products of twin pregnancy were referred to the endocrinologist for further work ups regardless of their screening TSH results. For each patient, gestational age, birth weight, birth season and the results of TSH measurements were recorded. The data were analyzed by SPSS version 19. Regression tests were used to analyze our data.

Results

During 5 years, 119701 neonates were screened for CH in Guilan province. Referral rate was 1.7% (2035 cases) of the total screened neonates. Congenital hypothyroidism was confirmed by serum TSH, T4 in 10.8% (221) of the referral cases which indicates that the prevalence of CH is 1:542 in this region.

Patient characteristics of all screened neonates are summarized in Table 1 to compare the distribution of the risk factors among neonates with CH and normal population. Some subjects had missing features in their old charts which are shown as missing data.

Table 1. Distribution of different factors among patients with Congenital Hypothyroidism (CH) compared to all screened neonates in Guilan province during 5 years (2006-2010).

Factor		CH		All screened neonate		CH/SN percentage and fraction		Comparison of distribution between CH and all neonate
		Number	%	Number	%	%	1/n	
Gender	Male	119	53.8%	60964	50.9%	0.20%	494	NS
	Female	102	46.2%	58738	49.1%	0.17%	598	
Gestational age	Preterm	5	2.3%	3113	2.6%	0.16%	623	In CH patients
	Term	210	95%	116348	97.2%	0.18%	554	Post date > preterm >
	Postdate	3	1.4%	240	0.2%	1.25%	80	term with
	Missing	3	1.4%	-	-	-	-	$P<0.01$
Birth weight	LBW-VLBW	30	31.7%	5865	4.9%	0.51%	196	In CH patients LBW
	Normal BW	171	77.4%	107971	90.2%	0.16%	631	> LGA > NBW
	LGA	16	7.2%	5865	4.9%	0.27%	367	with $P<0.01$
	Missing	4	1.8%	0		-	-	
Delivery route	C/S	138	62.4%	84745	70.8%	0.16%	614	In CH patients
	NVD	80	36.2%	34956	29.2%	0.23%	437	NVD> C/S with
	Missing	3	1.4%	0	-	-	-	$P<0.05$
Birth time	Spring	38	17.2%	25545	21.3%	0.15%	672	NS
	Summer	53	24%	30703	25.6%	0.17%	579	
	Autumn	59	26.7%	29415	24.6%	0.20%	499	
	Winter	71	32.1%	34038	28.4%	0.21%	479	
	Missing	0	-	-	-	-	-	
Referral TSH	<5	21	10%	-	-	-	-	-
	5-10	74	36%	-	-	-	-	
	10.1-20	37	18%	-	-	-	-	
	> 20	72	35%	-	-	-	-	
	Missing	17	-	-	-	-	-	
Total		221	-	119701	-	0.18%	542	

CH: Congenital hypothyroidism, SN: screened neonates, 1/n: means 1 case among "n" number of screened neonates, LBW: Low birth weight (birth weight <2500 g), NBW: Normal birth weight, LGA: Large for gestational age (birth weight >4000 g), NS: Not significant difference in distribution between patients with CH and normal population, Missing: subjects that had missing data in their old charts.

Table 2. Mean level of TSH in the screening tests in relation to different factors.

Factors		Number of neonates with available data	Mean Screening TSH (mu/l)	Explanation
Delivery route	NVD	74	18.4±23.5	NS difference
	Caesarean section	127	24.9±27.6	
Gestational age	Preterm	4	19.8±23.3	NS difference
	Term	164	22.8±27	
	Post date	3	37.3±25.7	
Birth weight	LBW (<2500 g)	30	18±28.1	NS difference
	Normal BW (2500 -4000 g)	157	23±26.2	
	LGA (>4000 g)	14	27.4±23.8	
Gender	Male	110	20.8±26.4	NS difference
	Female	94	25.4±27	

NS: Not significant, LBW: Low birth weight, BW: Birth weight, LGA: Large for gestational age, Small number of postdate and preterm cases may have interfered with these results.

Male gender, winter and caesarean section (C/S) have an apparently dominant proportion in neonates with CH but normal population has the same pattern and no significant statistical difference was seen. Regarding these data, the main distribution difference between neonates with CH and normal population was seen in birth weight and gestational age. CH was more prevalent in low birth weight (LBW) (31% of neonates with CH vs. 4.9% of normal population, $P<0.01$) and postdate delivery in comparison to normal population (1.4% of neonates with CH vs. 0.2% of normal population, $P<0.01$). Odds ratio of CH in a post-date delivery is 6.9 (Odds ratio range: 2.2-21.8). In LBW neonates odds ratio of CH are 3.2 (range 2.1-4.8). Macrosomia (LGA) with odds ratio of 1.7, has significant statistical difference among neonates with CH versus normal population ($P=0.035$). Rate of NVD was higher in neonates with CH compared to normal population (39.2% vs. 29.2% respectively, $P=0.01$). Mean referral TSH was 22.9 ± 26.7 mu/l (range: 1.1-130 mu/l). Most of these patients had TSH levels of 5-10 mu/l (74 cases: 36% of total), but weekly positive linear correlation was seen between screening TSH and repeated serum TSH (Pearson correlation: 0.37 with significance factor <0.01).

The mean of screening TSH was compared based on gender, delivery route, birth weight and gestational age none of which had a significant *P* value (Table 2).

Discussion

Congenital hypothyroidism (CH), one of the well known causes of mental retardation, is more prevalent among Iranian population than other populations (6,7). In recent years, establishment of a reliable screening program with a reasonable coverage of newborn in Iran has led to the early diagnosis and treatment of many neonates (8). Identification of risk factors for this condition can improve diagnosis or treatment plan of these neonates. Some studies have assessed multiple factors and their correlation in neonates with CH (9,10), but comparison of distribution of these factors between patients with CH and the whole population has not been well described.

The high prevalence of CH in different studies from Iran may indicate a different etiologic pattern and more exposure to risk factors or probably genetic susceptibility of Iranian population. Interestingly, there is some variation in different areas of Iran as well (6,7). In this study, high prevalence of CH (as much as 1:542) is about 3 times the prevalence of CH in Shiraz as concluded in other studies (1:1453) (7). All of these studies were performed when Iran was registered as a country free of iodine deficiency disorder (11). This difference may be due to diet or genetic difference and needs a well designed study to evaluate the role of these features. Some authors believe that caesarean section can influence TSH level in screening programs (12,13). Therefore, high rate of C/S in Iran may also be interpreted as a risk factor for high prevalence of CH. But by 3 methods of analysis, no data could be found to confirm this probability. 1. The rate of NVD in CH patients is higher than normal population (39.2% vs. 29.2% respectively, $P=0.01$). 2. Screening TSH levels showed no difference between C/S compared to NVD group. 3. And finally, the rate of CH among C/S group was 1:614 and was less frequent than NVD group (1: 437). As to the acceptable number of cases of CH, this study does not indicate the association or any risk relation between C/S and CH.

Despite the controversy about C/S, results of birth

weight and gestational age were similar to other studies, indicating that CH is related to LBW and postdate delivery (9,14,15). Analyses show an obvious increase in the incidence of CH in postdate neonates as much as 7 times of term neonates (Odds ratio: 6.9) with a prevalence of 1/80 among postdate neonates. However, this difference was not observed in the mean of screened TSH levels among these 3 categories. This discrepancy might be due to the small number of postdate and preterm cases. With review of literature and confirmation of this data we strongly recommend avoidance of postdate deliveries as much as possible, to keep close follow up of postdate neonates and to have a higher index of suspicious to CH in this group (16).

LBW neonates are at higher risk for CH than normal birth weight neonates (Odds ratio= 3.2). Screening TSH didn't show a significant difference between these groups either (Table 2). These high risk patients may have a different pattern of rising of TSH in hypothyroidism and more attention should be paid to them (14,15). In this study we didn't have enough follow up to rule out transient hyperthyrotropinemia but we agree with Hinton *et al.* who indicated that higher prevalence of CH among LBW may be the result of "delayed rise in thyrotropin concentration" (17). Macrosomia (LGA) also shows higher prevalence among CH patients; and on the other hand, CH is more prevalent in LGA neonates than neonates with normal weight. This difference is statistically significant compared to normal population (P=0.035) as was also mentioned by Waller *et al.* (16).

Based on the screening TSH results, most of the patients had TSH levels between 5-10 mu/l. It indicates that TSH ≥ 5mu/l is a good cut off point for screening program. Cases of CH with TSH < 5mu/l were neonates with LBW, any sick condition or a clinical picture suspicious to hypothyroidism. In conclusion, Guilan is an area with a high prevalence of CH. LBW, postdate pregnancy and macrosomia are risk factors for CH. No association was found between sex, birth season or caesarian section with CH.

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