

# Parental consanguinity among parents of neonates with congenital hypothyroidism in Isfahan

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## قراءة العَصَبَات بين آباء الوُلدان المصابين بقصور الدرقية الخلقي في إصفهان

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**الخلاصة:** حدّد الباحثون مدى انتشار قصور الدرقية الخلقي، ومعدل انتشار قرابة العَصَبَات بين آباء الوُلدان المصابين بقصور الدرقية لدى 93 381 ولداً، وُلدوا في 17 مستشفى في إصفهان، خلال الفترة من أيار/مايو 2002 إلى نيسان/أبريل 2005. وقيست مستويات ثيروكسين المصل (T<sub>4</sub>)، والهرمون المنبّه للدرقية (TSH)، خلال المدة من اليوم الثالث إلى اليوم السابع من الولادة. واستُدعي الوُلدان الذين وجدت مستويات القياس لديهم غير طبيعية، لإعادة تقييمها. واعتبر الوُلدان الذين كان مستوى الهرمون المنبّه للدرقية لديهم 10 ميلي وحدة دولية/ل أو أكثر، وثيروكسين المصل أقل من 6.5 ميكروغرام/دل، في المقايضة الثانية، مصابين بقصور الدرقية. وبلغ مجموع من استُدعي 1038 ولداً، شخّصت الإصابة بقصور الدرقية لدى 274 منهم. وتبيّن أن هنالك ترابطاً يُعتدُّ به إحصائياً بين قرابة الوالدين وبين الإصابة بقصور الدرقية الخلقي (P = 0.006). وكان قصور الدرقية الخلقي أكثر شيوعاً لدى الوُلدان الذين أبائهم أبناء عمومة من الدرجة الأولى، منه لدى الوُلدان الذين أبائهم أبناء عمومة من الدرجة الثانية (P = 0.008).

**ABSTRACT** We determined the prevalence of congenital hypothyroidism and the rate of consanguinity among parents of hypothyroid neonates among 93 381 neonates born in 17 hospitals in Isfahan from May 2002 to April 2005. Serum thyroxine (T<sub>4</sub>) and thyroid stimulating hormone (TSH) levels were measured on the 3rd–7th day of birth and neonates with abnormal levels were recalled and the levels reassessed. Those with TSH ≥ 10 mIU/L and T<sub>4</sub> < 6.5 µg/dL on the second assay were considered hypothyroid. In all, 1038 neonates were recalled and 274 were diagnosed as hypothyroid. There was a significant association between parental consanguinity and congenital hypothyroidism (P = 0.006); congenital hypothyroidism was commoner in neonates with 1st cousin parental consanguinity than 2nd cousin parental consanguinity (P = 0.008).

## Consanguinité parentale chez les parents de nouveau-nés présentant une hypothyroïdie congénitale à Ispahan

**RÉSUMÉ** Nous avons évalué la prévalence de l'hypothyroïdie congénitale et le taux de consanguinité chez les parents de nouveau-nés hypothyroïdiens dans un échantillon de 93 381 enfants nés dans 17 hôpitaux d'Ispahan entre mai 2002 et avril 2005. La thyroxine (T<sub>4</sub>) et la thyroïdostimuline, ou TSH (*pour thyroid stimulating hormone*), sériques ont été mesurées entre les 3<sup>e</sup> et 7<sup>e</sup> jours de vie, les nouveau-nés présentant des taux anormaux étant alors rappelés pour un nouveau dosage hormonal. En présence d'une TSH ≥ 10 mIU/L et d'une T<sub>4</sub> < 6,5 µg/dL, le diagnostic d'hypothyroïdie était alors confirmé. Nous avons recensé au total 1038 rappels de nouveau-nés et 274 cas d'hypothyroïdie avérée. L'association entre consanguinité parentale et hypothyroïdie congénitale est apparue significative (p = 0,006). Nous avons constaté une plus grande fréquence de l'hypothyroïdie congénitale chez les nouveau-nés issus de mariages entre cousins germains que chez les enfants nés de mariages entre cousins issus de germains (p = 0,008).

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## Introduction

Congenital hypothyroidism is one of the most preventable causes of mental retardation. Its prevalence is reported to be 1 in 3000–4000 live births. Early diagnosis and treatment of congenital hypothyroidism can prevent its hazards [1].

The prevalence of congenital hypothyroidism varies in different areas and among different races. Previous studies have shown that congenital hypothyroidism was more prevalent among Asian neonates than others and parental consanguinity was considered as a cause [2,3]. Besides familial factors, other risk factors, such as environmental, genetic and autoimmune factors, affect the prevalence of congenital hypothyroidism [4–7].

Congenital hypothyroidism has been reported to be more prevalent in the Islamic Republic of Iran than other communities. Three studies in our country, in Fars province, Tehran and Isfahan, have reported a high prevalence of congenital hypothyroidism [8–10]. Moreover, recently Ordookhani et al. reported a high prevalence of permanent congenital hypothyroidism and parental consanguinity among patients with congenital hypothyroidism in Tehran [11].

The aim of our study was to determine the prevalence of congenital hypothyroidism in our region by screening for the disorder in Isfahan. According to the preliminary findings of the study of Hashemipour and colleagues [10], the prevalence of congenital hypothyroidism is high in our region. Therefore, as well as determining the prevalence of congenital hypothyroidism, we compared parental consanguinity of all referred neonates with that of neonates with confirmed congenital hypothyroidism to determine if this factor plays a role in the disorder.

## Methods

This was a descriptive study carried out from May 2002 to April 2005 and all neonates referred from the 17 maternity hospitals in Isfahan were evaluated. The study was designed in collaboration with paediatric endocrinologists, the head of the Isfahan Endocrine and Metabolism Research Centre, the head of the Social Medicine Department of Isfahan University of Medical Sciences and Health Services and carried out with the research assistance of Isfahan University of Medical Sciences & Health Services. The Research Bureau of Isfahan University of Medical Science and Health Services gave ethical approval for the study.

The deans of all the 17 hospitals and the heads of their neonatal sections were informed of the study, and the importance of screening for congenital hypothyroidism was explained. With their approval, we approached all newly delivered mothers in the hospitals and explained to them the disorder, its complications and the method of screening. The coverage percentage of this project was derived by calculating the ratio of the number of referred neonates to live births.

Trained nurses in the hospitals completed a questionnaire with mothers which recorded gestational age, neonate's sex, weight, height, head circumference and nationality and parental consanguinity (1st and 2nd cousin). We recommended that the mothers attend the Isfahan Endocrine and Metabolism Research Centre for screening after discharge from hospitals on the 3rd–7th day of delivery. They were requested to give the questionnaire to the executive committee of congenital hypothyroidism screening in the Centre. This committee consisted of a trained general practitioner and nurses who received the referred women.

Venous blood samples of the neonates were obtained by trained nurses in the Centre on the 3rd–7th day of birth and serum thyroxine ( $T_4$ ) and thyroid stimulating hormone (TSH) levels were measured in Isfahan Endocrine and Metabolism Research Centre. An endocrinologist and collaborating general practitioner evaluated the laboratory results, the status of parental consanguinity and determined the neonates who needed to be recalled.

Recalls were determined based on the levels of  $T_4$  and TSH in neonates born at term who weighed over 2500 g. Neonates born at term with  $T_4 < 6.5 \mu\text{g/dL}$  or TSH  $\geq 20$  mIU/L [12,13], and premature neonates with a low level of  $T_4$  for their weight or high TSH level for their age were selected for recall [14]. Neonates who were referred after the 7th day of birth were recalled based on a  $T_4$  level  $< 6.5 \mu\text{g/dL}$  or TSH level  $> 10$  mIU/L [15].

If the TSH level was between 20 and 39 mIU/L then a second laboratory test, including  $T_4$ , was carried out. If the TSH level was  $> 40$  mIU/L then as well as carrying out a second laboratory tests, treatment was initiated [16]. The second measurement from recalled neonates was performed on the 7th–28th day of birth. According to the 2nd laboratory test, if the levels of TSH and  $T_4$  were in the normal range, the neonate was considered to have hyperthyrotropinaemia. If the level of  $T_4$  was  $< 6.5 \mu\text{g/dL}$  or TSH  $> 10$  mIU/L [12] then the neonate was considered to have congenital hypothyroidism.

The physician performed physical examinations of the neonates and evaluated the laboratory tests and finally, based on the findings, prescribed levothyroxin 10–15 g per kg per day for hypothyroid neonates.

In addition to measurement of TSH level, if term or premature neonates had low levels of  $T_4$  according to their weight, additional laboratory tests, such as  $T_3$  resin

uptake ( $T_3\text{RU}$ ) and free  $T_4$  index ( $\text{FT}_4\text{I}$ ), were carried out. According to these results, congenital hypothyroidism was diagnosed and patients underwent treatment. Patients with confirmed congenital hypothyroidism were recommended to undergo thyroid scintigraphy before starting treatment.

### Laboratory methods

The levels of TSH and  $T_4$  were measured using Iran Kavoshyar kits. The level of TSH and  $T_4$  were measured using immunoradiometric assay and radioimmunoassay respectively with the gamma counter of the Endocrine and Metabolism Research Centre (Berthold LB 12-2111). Sensitivity of the kits was 0.05 mIU/L for TSH and 0.38  $\mu\text{g/dL}$  for  $T_4$ .

Thyroid scintigraphy was performed using technetium pertechnetate.

### Statistics

Data were analysed using SPSS, version 13 and Epi-Info, 2002. Differences in the frequency of parental consanguinity between screened neonates without congenital hypothyroidism and those with congenital hypothyroidism were compared using the chi-squared test. The odds ratios (OR) and confidence intervals (CI) for parental consanguinity in neonates with congenital hypothyroidism and those without were calculated.  $P < 0.05$  was considered significant.

### Results

This study included 93 381 neonates from 17 private and public maternity hospitals in Isfahan which represented 82.8% of live births. Of the neonates, 51.7% were female and 48.3% male, 97% were born at term and 3% premature, and 97.3%, 2.6% and 0.1% were respectively Iranian, Afghan and oth-

er nationalities (Armenian, Iraqi, Libyan, Yemeni); the nationality of 136 neonates was not determined.

Of all the studied neonates, 27.7% had parental consanguinity (both 1st and 2nd cousin); the parents of 61.6% of this group had a consanguineous marriage with a 1st degree relative. Of the 93 381 referred neonates, 1038 (1.1%) were recalled; 971 (93.5%) of these underwent laboratory tests and 274 were diagnosed with congenital hypothyroidism and received medical treatment.

The prevalence of congenital hypothyroidism was 2.9 per 1000 live births or 1 in 341 live births; 4 neonates had secondary hypothyroidism. As regards sex, 161 (58.8%) of hypothyroid neonates were female and 113 (41.2%) male, giving a female to male ratio of 1.4:1. Of the hypothyroid neonates, 251 (91.2%) were born at term and 23 (8.4%) were premature.

The rate of parental consanguinity (1st and 2nd cousin) is shown in Table 1; 101 (36.9%) neonates with congenital hypothyroidism had consanguineous parents (both 1st and 2nd degree relation) and of these, 75 (74.3%) had parental consanguinity with a 1st degree relation.

Only 121 (44.1%) of the hypothyroid neonates underwent thyroid scintigraphy (most of them were the patients with primary high TSH levels); the remainder did not undergo the procedure because of poor compliance of their parents. According to

the results of the thyroid scan, 82 (68.3%) of the patients with congenital hypothyroidism had a normal thyroid scan, 1 had goitre, 7 (5.8%) had ectopia and 31 (25.8%) had agenesis. Therefore 31.6% of our patients with congenital hypothyroidism had dysgenesis.

The overall prevalence of parental consanguinity among normal, goitrous, ectopic and agenetic congenital hypothyroidism patients was 46.3, 0.0%, 57.1% and 45.1% respectively. Data about 1st and 2nd cousin parental consanguinity among these patients are presented in Table 2.

There was significant association between parental consanguinity (both 1st and 2nd degree relation) and the prevalence of congenital hypothyroidism. Consanguinity was more prevalent among neonates with hypothyroidism (OR = 1.53, 95% CI: 0.51–0.85,  $\chi^2 = 11.33$ ,  $P = 0.0007$ ). In addition, congenital hypothyroidism was more prevalent in neonates with 1st cousin parental consanguinity as compared with 2nd cousin parental consanguinity (OR = 1.8, 95% CI: 1.13–2.88,  $\chi^2 = 6.83$ ,  $P = 0.008$ ).

## Discussion

The prevalence of congenital hypothyroidism worldwide is reported to be 1 in 3000–4000 live births [1]. In our study of 93 381 referred neonates the prevalence of congenital hypothyroidism was 1 in 349 live

Table 1 Parental consanguinity in all studied newborns and those with congenital hypothyroidism

	1st cousin parental consanguinity	2nd cousin parental consanguinity	No familial marriage	Total <sup>a</sup>
Total unaffected neonates	15 900	9916	67 251	93 067
Hypothyroid neonates	75	26	173	274

<sup>a</sup>For 40 infants it was not known if there was parental consanguinity or not.

Table 2 Parental consanguinity among patients who performed thyroid scintigraphy

Parental consanguinity	Normal (n = 82)		Thyroid scintigraphy					
	No.	%	Goitre (n = 1)		Agenesis (n = 31)		Ectopia (n = 7)	
	No.	%	No.	%	No.	%	No.	%
1st cousin	31	37.8	0	0.0	12	38.7	3	42.9
2nd cousin	7	8.5	0	0.0	2	6.4	1	14.3
Overall	38	46.3	0	0.9	14	45.1	4	57.1

births, which is high. Previous studies have reported a high prevalence of congenital hypothyroidism in our country (1 in 1433, 1 in 914 and 1 in 370 live birth in Fars province, Tehran and Isfahan respectively) [8–10]. Rates for nearby countries differ. The prevalence of congenital hypothyroidism in Pakistan was reported to be 1 in 1000 live births [17], while in Saudi Arabia urban areas it was 1 in 2759 live births and in the rural areas it was 1 in 1538 live births [18].

Our study shows that among neonates with congenital hypothyroidism, parental consanguinity was 1.5 times higher than among neonates without congenital hypothyroidism. Various studies have reported that congenital hypothyroidism is more prevalent among Asian families than non-Asian ones. Rosenthal et al. evaluated the prevalence of congenital hypothyroidism in the north-west of the United Kingdom (UK) among different races, nationalities and minorities, especially Muslims and Asians [2]. They found that the prevalence rates of congenital hypothyroidism among Asians and non-Asian families were 1 in 918 and 1 in 3391 live births respectively. This significant difference may be a result of parental consanguinity among the Asian population. Congenital anomalies, mortality and morbidity were also more prevalent in hypothyroid neonates [2]. Another study in the UK, from 1981 to 1991 showed that the

prevalence of congenital hypothyroidism among Pakistani families with consanguineous parents (1 in 781 live births) was significantly higher than the total prevalence of congenital hypothyroidism in the UK (1 in 2154 live births) [3]. In addition, congenital hypothyroidism prevalence among Indian neonates without consanguinity was 1 in 5540 live births.

A study in Israel showed that the incidence of congenital hypothyroidism was higher in Arab families with familial marriage than those reported from industrialized countries, but was similar to those found in Saudi Arabia [19]. This may be due to the high degree of consanguineous marriages among Arab populations. Also a study in Saudi Arabia found that congenital hypothyroidism was 1.8 times more common in rural areas and they believed that consanguinity was the cause [18]. Ordookhani and colleagues have shown high prevalence of familial marriage among cases of congenital hypothyroidism [11]. Only a few studies have shown no significant relationship between consanguinity and congenital hypothyroidism [20]. Overall these findings suggest a role of consanguinity in congenital hypothyroidism and other congenital anomalies.

Recently Ordookhani and colleagues reported a high prevalence of consanguinity among patients with permanent congenital

hypothyroidism [21]. They concluded that parental consanguinity may be considered a causative factor for the high prevalence of thyroid dysgenesis, which was the commonest cause of permanent congenital hypothyroidism in their study. Overall, 28.6% of all screened neonates and 47.1% of hypothyroid patients had parental consanguinity. Our findings (27.7% of all studied neonates and 36.9% of congenital hypothyroidism patients with consanguineous parents) are similar to these.

In our study, parental consanguinity, especially with 1st cousin relation, was more prevalent among hypothyroid neonates. We did not study the prevalence of transient and permanent hypothyroidism because our patients with congenital hypothyroidism had not reached 3 years of age which is necessary for determination of transient and permanent forms of congenital hypothyroidism. Nonetheless, our findings support the role of consanguinity in the high prevalence of overall congenital hypothyroidism.

According to our study, overall parental consanguinity and 1st cousin parental consanguinity were present in 47.4% and 39.5% of all infants with dysgenesis (agenetic and ectopic), which is in line with the results of a recent study in Tehran [10] which reported overall and 1st cousin parental consanguinity of 55.6% and 33% among congenital hypothyroidism patients with dysgenesis. Although the rate of transient and permanent congenital hypothyroidism has not yet been determined, patients diagnosed with dysgenesis are considered permanent congenital hypothyroid. The remainder with normal thyroid scan can be considered

transient pending additional studies that will be performed at 3 years of age.

Considering different etiologies of congenital hypothyroidism, dysmorphogenesis is inherited through an autosomal recessive pattern but dysgenesis is a sporadic disorder. The causes of thyroid dysgenesis are unclear, but are believed to be multifactorial, including environmental and complex gene interactions [22]. A recent study has reported that familial factors affect 2% of all dysgenesis cases [23].

As with the study of Ordookhani et al., nearly half of our patients with congenital hypothyroidism with dysgenesis had parental consanguinity which has not been reported by other studies. This may reflect the presence of some unknown mutations in the genes involved in thyroid ontogeny in our population.

Considering the high prevalence of congenital hypothyroidism in our country, consanguinity, especially with first degree relatives, clearly appears to have a role in this increased prevalence. More studies are needed in this area. At the same time, interventions are needed to try and reduce the rate, such as public awareness activities to increase people's knowledge about the condition and the risk of familial marriage.

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#### **Child and Adolescent Health and Development website**

This website aims at sharing information on the work on the health and psychosocial development of children under-5 carried out by the WHO Regional Office for the Eastern Mediterranean and related activities and initiatives promoted and carried out in countries in the Region. It is intended for public health and programme managers, academia, civil organizations and nongovernmental organizations, students and anyone interested in public child health issues, with special focus on the Eastern Mediterranean Region.

The CAH website provides detailed information on the coverage of child health activities at different levels in countries in the Region, especially the implementation of the Integrated Management of Child Health (IMCI) strategy. Specific sections describe the evolution of IMCI over the years in the Region, the process and guidelines to develop national child health policies, work carried out in the area of pre-service education related to child health, health systems issues, the community component, the child health-related Millennium Development Goals, research work, and advocacy initiatives.

The website can be accessed at: <http://www.emro.who.int/cah/>