Seasonal variation in the incidence of congenital hypothyroidism in Isfahan, Iran

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ABSTRACT

Objective: To evaluate the seasonal variations in the incidence of congenital hypothyroidism (CH) in the screening program of CH in Isfahan, Iran.

Methods: In this study, we compiled the data obtained retrospectively from CH screening results of 113282 neonates from 17 maternity hospitals in Isfahan, Iran from June 2002 to December 2005. The seasonal variation in the incidence of CH, as well as its monthly incidence was analyzed using all the diagnosed cases of CH.

Results: From the 113282 neonates referred for CH screening, 358 neonates were diagnosed with CH, showing an overall incidence of 3.1/1000 live birth. There was no significant difference in the seasonal variation of CH (p=0.5). According to the monthly distribution analysis, the incidence of CH was higher in the second month of summer (Mordad) and lower in the last month of autumn (Azar)(p=0.04).

Conclusion: The high incidence of CH in Mordad, the second month of summer, supports the hypothesis that certain environmental factors such as intrauterine viral infections (which commonly exhibit seasonal variations in incidence), exposure to chemical compounds, differences in climate and so forth, may play a role in the etiology of this disorder. Awareness of the monthly distribution of CH incidence could help us identify associated environmental factors and aid in the development of preventative strategies. Further, it would for the appropriate allocation of resources within the screening programs.

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Congenital hypothyroidism (CH) is reported to affect one in 3000-4000 newborns, making it the most common congenital endocrine disorder. Neonatal screening programs for CH allow early diagnosis of the condition and subsequent treatment with the exogenous thyroid hormone. This efficiently prevents the complications associated with untreated CH and thyroid hormone deficiency, such as mental retardation. The CH patients have an abnormality in the development of the thyroid gland dysgenesis or thyroid dyshormonogenesis.[1] The incidence of CH has been shown to vary among different parts of the world. This results came from both genetic and environmental factors. The genetic basis of CH is reported by many previous studies, and several genetic defects have been mapped and recognized to be associated with both thyroid dyshormonogenesis and dysgenesis.[2] Immunologic, environmental, and iatrogenic factors are also known to induce CH.[2] Studies on seasonal variation of CH have suggested that the causes of CH are not only intrinsic factors such as immune system dysfunction or gene defects, but environmental factors also play a role. However, there is a controversy regarding the effect of seasonal variation in the incidence of CH. While some previous studies have reported a certain degree of seasonal variation in the incidence of CH,[3-7] other studies have not confirmed this.[8] Miyai et al[9] demonstrated the seasonal incidence of CH in the Osaka area in Japan and proposed a hypothesis that an unknown environmental factor may be the cause of the disease. Subsequent studies also revealed that the seasonal incidence of the disease was observed in some areas (Japan, Australia, Quebec, and Toronto), but the seasons were not identical and the sane seasonality could not be found in other areas

(Pennsylvania, Norway, France, and Switzerland). In one study in Tehran, Iran higher incidence of CH in the winter has been reported.[4] On the contrary, no significant seasonal variation in the incidence of CH was observed in other studies such as those of Childs and Gardner in Japan,[10] Kaiserman et al in Israel,[5] and Rocchi et al in Italy.[11] We therefore conducted this study to assess whether there is any association between season of birth and the incidence of CH particularly in Isfahan, Iran. If this should be the case, the data would be useful in the development of CH preventive strategies and the allocation of resources in the CH screening program accordingly. Therefore, considering the high prevalence of CH reported in Isfahan,[12] this study was preformed to assess the probable variations in the incidence of CH in different seasons.

Methods. In this study, we used the data collected from the CH screening of 113282 neonates from 17 maternity hospitals (private, public, educational, and the township) in Isfahan, Iran from June 2002 to December 2005. This study was approved by Isfahan Endocrine and Metabolism Research Center ethics committee. The CH screening program in Isfahan begun in June 2002 and continues to operate. In accordance with the screening protocol, we referred neonates for screening on their third to seventh day of life. Serum concentration of thyroxin (T4) and thyroid stimulating hormone (TSH) are drawn through ante-cubital venous sampling by trained nurses. A questionnaire is completed with each neonate's gender, height, weight, date of birth, and maternal age at pregnancy. After physical examination, and verification of the laboratory data, a team consisting of pediatric endocrinologist and general practitioners determined which neonates had to be recalled. Neonates referred between the third to seventh days of life were recalled in the case of having a TSH >20mIu/L or a T4 <6.5 mg/dl. Those neonates who were referred after the seventh day of life were recalled in the case of having a TSH >10mIu/L or a T4 <6.5 mg/dl. Among recalled neonates, if the level of TSH at the first measurement were >40 mIu/L, then secondary laboratory tests and treatment was performed simultaneously, but in the case of a TSH concentration between 20-39 mIu/L in the first measurement, only secondary laboratory test was performed. These tests, conducted on the seventh to twenty-eighth day of life, included the measurement of both TSH and T4 levels. Neonates were considered to be hypothyroid if they had a T4 <6.5 mg/dl or a TSH >10mIu/L. Hypothyroid neonates were treated with levothyroxine (10-15 mg/kg/day) and followed up according to a standard schedule.[13-17] The serum T4 was measured by radioimmunoassay and TSH by immunoradiometricassay methods, using the Iran Kavoshyar Co. Kit (Tehran, Iran) and by the gamma counter of Isfahan Endocrine & Metabolism Research Center (Bert hold IB 2111-12). Seasonal variation of CH and its incidence per month, among all diagnosed CH patients were evaluated using Statistical Package for the Social Sciences software (version 12) employing the χ^2 test.

Results. Of the 113282 neonates 1107 neonates were recalled, and 358 (32.6%) of the recalled neonates were diagnosed with CH. The characteristics of diagnosed CH patients are presented in **Table 1**. It shows an overall CH incidence of 3.1/1000 live birth. The seasonal variation of CH is presented in **Table 2**. The incidence of CH in spring was 3.2, summer 3.3, autumn 2.8 and winter 3.3 in 1000 live births and there was no significant difference in the seasonal incidence of CH (p=0.5). Although the incidence of CH was lower in the autumn, this difference was not statistically significant between seasons. The incidence of CH in each month is presented in **Table 2**. The CH had increased incidence in "Mordad" (23 July - 23 August) the second month of summer and decreased incidence in "Azar" (23 November - 23 December) the last month of autumn (4/1000 live birth versus 2.3/1000 live birth, p=0.04).

Discussion. Despite the high prevalence of CH in Isfahan, the analysis of the incidence of new cases with respect to the season and month of birth showed no statistically significant difference. However, increases and decreases in the incidence were noted in the summer and autumn, but the magnitude was not great enough to satisfy the statistical significance in this study. Studies in seasonal and chronological distributions of CH had controversial results in different countries. While some studies have shown a seasonal variation in the incidence of CH, with suggestions that some environmental factors

Table 1 - Characteristics of neonates diagnosed with congenital hypothyroidism by the screening program in Isfahan, Iran (2002-2005) (N=358).

Characteristics	n (%)	Mean ± SD
Maturity (term nenates)	322 (89.9)	
Parental consanguinity	119 (33.2)	
Weight (gr)		2906.3 ± 625.5
Height (cm)		48.6 ± 3.3
Head circumferences (cm)		34.1± 2.3
T4 (µg/dL)		7.01 ± 3.43
TSH (mIU/L)		43.2 ± 61.8

T4 - serum concentration of thyroxin
TSH - thyroid stimulating hormone

such as viral infections (for example varicella-zoster), food, chemical compounds (such as polychlorinated biphenyls or dioxins), climate changes and iodine deficiency may be a contributing factor in the etiology of CH,[9,18,19] others did not confirm such seasonal variation in the occurrence of CH.[8,20,21] From the aforementioned risk factors of CH, only the issue of iodine deficiency has been addressed in recent years.[22] According to a study in Isfahan, the mean urinary iodine concentration of neonates was 21.53±7.83 µg/dl which demonstrated that currently Isfahan is an iodine replete area, and so iodine deficiency is not a contributing factor in the etiology of CH.[23] Other environmental factors in our region and their effect on CH have not been studied yet. It seems that the findings of this study could help us to design our future studies to identify further implicating factors. The seasonal variation in the incidence of CH has been analyzed in 8 areas of the world, and such seasonal variation in the incidence has been shown.[9]

In 1954, Childs and Gardner[10] reported that the occurrence of CH had no significant seasonal variation. Rosenthal et al [20] did not detect any seasonality for CH occurrence in the North-West England. No evidence of seasonal variation was also observed during CH screening program in the Kingdom of Saudi Arabia.[21] During a 10-year temporal analysis of CH in Israel, a non-periodic etiology for sporadic primary CH was reported.[5] In a recent study in Italy, the role of date of birth as a risk factor for CH was studied among 92 CH patients during 15 years. This study showed that neither the hypothesis of date of birth as a risk factor for CH, nor the existence of seasonal variations in TSH release was confirmed.[11] In addition, many studies have reported a variety of seasonal variations for the incidence of CH in various countries. The CH occurrence was even different in the same geographic area during different periods of time. The incidence of CH was higher in the summer during 1957-1976 in Osaka, Japan but it was higher in the late autumn in the same area according a recent study.[9,24] NaKamizo et al[18] reported higher occurrence of CH in the winter and lower occurrence of CH in the spring and autumn. They concluded that environmental factors, especially chemical compounds are notable risk factors for CH, though there is little evidence that these factors are the cause of CH. In West-Midland, the incidence of CH was higher in the autumn (between October-December).[3] In Austria, the incidence of CH was higher during September-November.[25] Virtanen et al[7] found both geographical and seasonal variations in the CH in Finland.[7] Ordookhani et al[4] reported increased incidence of CH in the winter in Iran, 2.9 times higher than the mean of the others 3 seasons combined. In our study, the lowest occurrence of CH was seen in the autumn, but this difference was not statistically significant. The monthly occurrence of CH was higher in midsummer and less common in late autumn. Considering the vast differences between our study as well as the results of other studies in seasonal variation of CH incidence, we conclude that the reasons for these differences are multifactorial. For example, differences in climate, viral infections or chemical compound exposures may all be contributing to different degrees in different geographic areas. The effect of all these factors warrants further study. For example, according to some studies, intrauterine infections of the fetus in early pregnancy, induces certain congenital anomalies such as CH.[26-29] In addition, the development of the thyroid gland during the fetal period occurs in the first 3 months of gestation. Considering that in our region CH had increased incidence in Mordad (July-August), and less common in Azar (October-Novels), it suggests that environmental factors might have the greatest effect on fetal thyroid gland development in late autumn. This could help us to determine the risk factors responsibly for the monthly variations in CH incidence.

Table 2 - Seasonal and monthly distribution of congenital hypothyroidism (CH) during CH screening in Isfahan, Iran (2002-2005).

Seasons/months	CH patients	Screened neonates	Incidence (per 1000 live birth)	Incidence (per 1000/ birth)
Season (1) Spring	88	26124	3.4	
Farvardin	26	8292		3.1
Ordibehesht	27	7908		3.4
Khordad	35	10824		3.2
Season (2) Summer	110	33545	3.3	
Tir	35	11402		3.1
Mordad	43	10761		4
Shahrivar	32	11382		2.8
Season (3) Autumn	78	28247	2.8	
Mehr	32	10228		3.1
Aban	27	9791		2.8
Azar	19	8228		2.3
Season (4) Winter	82	24466	3.3*	
Day	31	8280		3.7
Bahman	26	8370		3.1
Esfand	25	7816		3.2†

* p=0.5 between seasons, † p=0.000 between months
Seasonal 1 - 21 March - 20 June, Seasonal 3 - 21 June - 21 September
Seasonal 3 - 22 September - 22 December,
Seasonal 4 - 23 December - 20 March

In conclusion, our findings show that there was no significant difference in the seasonal incidence of CH. Therefore, resource allocation for our nationwide CH screening program which started in 2006 should remain equivalent in all months. On the other hand, the monthly distribution of CH could be used to provide further studies in this field and aid us to develop more preventative strategies, such as influenza vaccinations, or pollution control. Our study carry certain limitations. One such limitation was its duration. Although the incidence numbers of CH were high, and the number of studied patients seemingly large, for more accurate conclusions and improved statistical power, the study would need to be conducted over a longer time after initiation of the screening program. For example, 10-15 years period would be in closer keeping to comparable studies. Another limitation of our study was the inability to differentiate between the transient and permanent forms of CH. Since our screening program began in 2002, most of our participants were studied in the first 3 years of their life. However, in order to diagnose permanent forms of CH, thyroid hormone therapy needs to be withheld for a period of 4 weeks after the age of 3, at which time TSH and T4 levels are drawn. Therefore, we could not distinguish between transient and permanent cases of CH for our study. Therefore for future studies, these limitations would be excluded by virtue of our screening program having existed over a longer time. In addition, it is well known that genetic factors play a role in the etiology of CH. Considering that the rates of consanguinity are relatively high in our community, this could be one reasons why the incidence of CH in Isfahan was high as reported earlier.[30] Further, studies are needed to investigate the suggested role of the gene-environment interactions in the high prevalence of CH in our community and to better elucidate the relative significance of each in the etiology of CH.

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Related topics

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