



Original Article



Spatial Distribution of Congenital Hypothyroidism

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Abstract

Background: This study was designed and conducted to investigate the spatial distribution of permanent and temporary congenital hyperthyroidism (PCH and TCH) in Isfahan.

Methods: This study was conducted on neonates who were born from March 21, 2006 to March 20, 2011 and had undergone the congenital hypothyroidism (CH) screening program in counties affiliated to the Isfahan University of Medical Sciences. CH was diagnosed in 958 patients who treated with levothyroxine. The incidence rates of permanent and temporary congenital hypothyroidism in Isfahan province were calculated and their distribution was shown on the map. The space maps were drawn using the ArcGIS software version 9.3.

Results: Based on the data obtained from the screening program, the average incidence of congenital hypothyroidism in the province during the period of 2006–2011 was 2.40 infants per 1000 live births (including both PCH and TCH). The most common occurrence was in Ardestan County (10:1000) and the lowest overall incidence was observed in the Fereydounshahr county (1.39:1000). The incidence of PCH in the counties of Ardestan and Golpayegan had the highest rate in all years of study; and the greatest number of TCH cases in the five years were observed in Nain, Natanz, Khansar and Chadegan counties.

Conclusion: Adding the time dimension and performing spatial-temporal analysis is suggested because of the following items: high prevalence of CH in Isfahan province, the important role of this disease in mental retardation and neuropsychiatric disorder, the necessity of conducting future medical researches to find possible factors of CH etiology in Isfahan province, as well as necessity of performing spatial analysis with advanced statistical methods.

Keywords: Congenital hypothyroidism, Geographic Mapping, Permanent, Transient

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Introduction

Congenital hypothyroidism (CH) is one of the most common congenital endocrine disorders,¹ with a prevalence of 1 per 3000 to 4000 births.² It is divided into transient and permanent types and is a major cause of preventable mental retardation.³ In transient hypothyroidism, infants have normal or low serum thyroxine (T4)⁴ and increased serum thyroid-stimulating hormone (TSH) concentrations that may be restored with or without treatment,⁵ while patients with the permanent type require lifetime hormone therapy.⁶ Since early diagnosis and treatment of CH results in normal childhood in many cases of hypothyroidism,⁷ screening programs were developed in the early 1970s and have been accepted by many countries worldwide.⁸ In Iran, screening newborns for CH has been integrated into the National Public Health System and launched nationwide since 2005 using the protocol of TSH measured in heel prick blood spot samples in neonates within 3–5 days of birth.⁹ The main objective of this program is early detection and management of the affected newborns to prevent mental disability, reduce related costs and improve quality of life, and enhance the IQ of these neonates.^{10,11} The reported prevalence of CH varies in

different regions, such as 1:2736 in Turkey, 1:781 in Pakistan, and 1:10 000 in African Americans.¹² Moreover, the average incidence of CH worldwide is estimated at around 1 in 3000–4000 live births, which is higher in Iran compared to the worldwide average incidence of hypothyroidism.¹³ There are some variations in different areas of Iran such as Tehran and Isfahan, which have an average prevalence of CH at 1:914 and 1:338 live births, respectively.¹³ Several studies have investigated different prognostic factors for CH,^{14,15} indicating the influence of several genetic and environmental factors on the incidence of this disease.¹⁴ However, some questions remain unanswered about the epidemiology of CH, including the distribution of permanent and transient cases.¹⁶ No study has been conducted in Isfahan province to describe the geographic variation and spatial distribution of CH. Hence, the objective of our study was to illustrate the spatial distribution of the incidence of permanent and transient CH using the dataset from the national newborn CH screening information system during 2006–2011 in counties affiliated to the Isfahan University of Medical Sciences.

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Patients and Methods

This study used an applied ecological method. The study population consisted of all live neonates born in counties affiliated to the Isfahan University of Medical Sciences from April 2006 to the end of March 2011; those confirmed as having CH were followed until 3 years of age. Neonates with Guthrie TSH test ≥ 5 mU/L were recalled for further investigations; those with a TSH 5–9.9 mU/L were recalled for second TSH heel prick screening tests. Finally, those with a first TSH screening ≥ 10 mU/L and second TSH screening ≥ 5 mU/L were recalled for confirmatory venous sampling. The final diagnosis was made by a pediatric endocrinologist, appointed as the focal point of the CH program in each county. Neonates with TSH >10 mU/L and/or TT4 (total thyroxin) <6.5 $\mu\text{g/dL}$ in venous samples were diagnosed as having hypothyroidism¹⁷ and promptly attended to and treated by an endocrinologist. The protocol of detecting, management and follow-up is described in the national guideline.¹⁷ Technical experts of each screening center routinely register the complete data of diagnosis, management and follow-up visits of the affected neonates from birth to their last visit at the age of 3 years in related healthcare forms provided by the Ministry of Health.^{17,18} All findings of the current survey are based on the data extracted from the completed central healthcare forms obtained from each region. The annual incidence rates of CH were calculated as numbers of definitely diagnosed CH (permanent and transient) among all live births during one year and expressed as numbers per 1000 live births for each county. After entering the data in MS-Excel pages, drawing of the maps and spatial analysis were done using ArcGIS 9.3 software. Spatial analysis is a series of statistical methods in which the objective is to gain a precise estimation of incidence, prevalence, survival, or mortality rate of phenomena. In recent decades, methods have been developed to obtain geographical pattern and determine low- and high-risk regions for both communicable and non-communicable diseases. Health designers apply spatial analysis to recognize environmental risk factors, plan for higher quality interventions and help disease prevention.¹⁹ In Arc Map, information was entered to the attribute tables of each polygon layer and then choropleth maps with quantile classified were drawn as a raster layers in five categories and hot spots were determined. Hot spot analysis is a great statistically-based tool to assess geographic clustering. Specifically, hotspot analysis is used to pinpoint locations of statistically significant high- and low-value clusters. These clusters are determined by evaluating each area within the context of neighboring areas and against all areas in the dataset. An area with high value is not necessarily a hot spot; it becomes a hot spot only when its neighbors also have high values, as opposed to simply being a data outlier. The local means for an area and its neighbors are compared proportionally with the global mean of all areas. When the observed local mean is much different than the global mean, where

difference is too large to be the result of random chance, a statistically significant z score results and a hot spot cluster is detected.²⁰

Results

From April 2006 to the end of March 2011, a total of 396 949 newborns were born in counties affiliated to the Isfahan University of Medical Sciences, and 958 of them were diagnosed with congenital hypothyroidism and treated with levothyroxine. According to the data obtained from the screening program, the incidence of CH was 3.00 (95% CI: 1.67–4.32), 3.44 (95% CI: 1.71–5.17), 4.96 (95% CI: 3.50–6.43), 3.26 (95% CI: 1.82–4.71), 2.34 (95% CI: 1.22–3.45), 3.43 (95% CI: 1.97–4.89) per 1000 live births in 2006, 2007, 2008, 2009, 2010, and 2011, respectively, showing an increasing trend from 2006 to 2008 and a decreasing trend from 2008 to 2010 (Figure 1). The results showed a high incidence of CH in counties affiliated to the Isfahan University of Medical Sciences that was equal to 2.40 (95% CI: 1.83–2.98) per 1000 live births, which includes both transient and permanent forms of the disease. The greatest incidence was found in Ardestan county with 10 (95% CI: 4.76–15.25) per 1000 live births, while the lowest overall incidence was observed in the Fereydounshahr County with 1.39 (95% CI: -0.45–3.24) per 1000 live births. PCH constituted 50% of the total cases of hyperthyroidism in the duration of the study, and 417 (50%) were diagnosed with temporary congenital hyperthyroidism (TCH). Figure 2 shows that the incidence of PCH in the counties of Ardestan and Golpayegan had the highest rate in all study years. The highest incidence rates pertained to Ardestan, Golpayegan, Khansar and Fereydan in 2006, to Ardestan, Chadegan, Khomeinishahr, Khansar, Fereydan, Falavarjan and Golpayegan in 2007, to Ardestan, Golpayegan, Khomeinishahr, and Dehaghan in 2008, to Ardestan, Golpayegan, Tiran & Crown in 2009, to Golpayegan, Ardestan and Khomeinishahr in 2010, and to Khansar, Ardestan, Natanz, Golpayegan, Semirom, Khomeinishahr, Lenjan, Shahreza, Borkhar & Meimeh in 2011. The most frequent cases of TCH in the last 5 years were in counties such as Nain, Natanz,

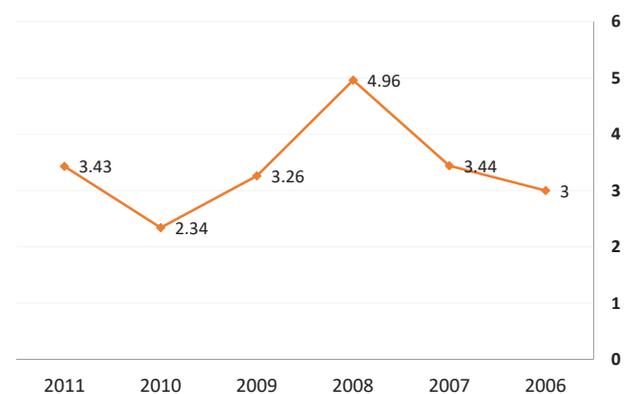


Figure 1. Trend of Incidence of Congenital Hypothyroidism During April 2006 to the End of March 2011.

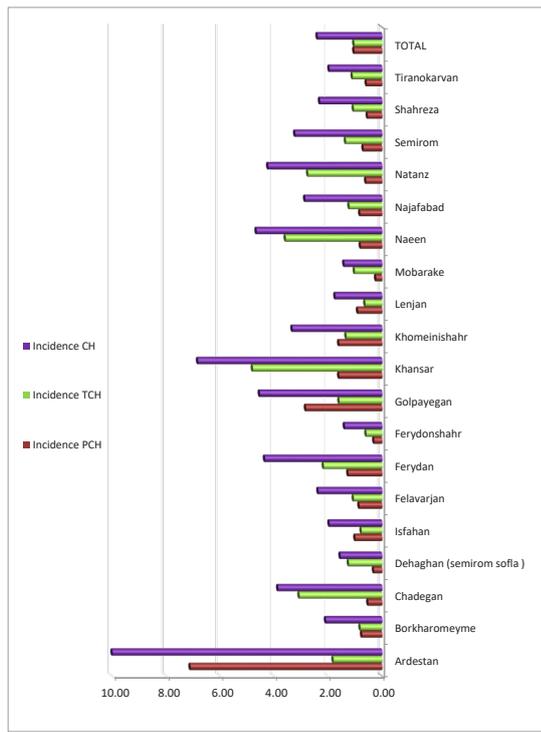


Figure 2. Hypothyroidism Incidence Rate for Each Town (2006–2011).

Khansar and Chadegan. The lowest incidence of TCH in the study period was observed in cities like Borkhar & Meymeh, Lenjan, Fereydounshahr and Isfahan. The lowest incidence of PCH occurred in Mobarakeh, Dehaghan and Fereidounshahr.

Discussion

The results of this study indicate a high incidence of CH in Isfahan province, which is 2.40 (95% CI: 1.83–2.98) per 1,000 live births; the incidence of CH was 3.00 (95% CI: 1.67–4.32), 3.44 (95% CI: 1.71–5.17), 4.96 (95% CI: 3.50–6.43), 3.26 (95% CI: 1.82–4.71), 2.34 (95% CI: 1.22–3.45), 3.43 (95% CI: 1.97–4.89) per 1000 live births from 2006 to 2011. The average incidence of CH worldwide is estimated at around 1 in 3000–4000 live births, which is higher in Iran compared to the average incidence of hypothyroidism in the world.¹³

There are some variations in different areas of Iran; for instance, in Tehran, Isfahan, Markazi province and Yazd (central cities of the country), the average prevalence rates of CH are reported at 1:914, 1:338, 1:307 and 1:1608 live births, respectively.^{13,21,22} The incidence of CH in Ardabil was found to be 1:916,²³ whereas in the north of Iran, it was estimated at 1 per 491 live births.²⁴ Nevertheless, the prevalence of CH in Iran is higher than other countries.^{21,25,26} In Korea, over the past 10 years, an increasing trend has been observed in the incidence of CH.²⁷ The incidence of CH has increased significantly in the Republic of Ireland over the past 37 years, despite having a consistent screening cut-off value. The increased rate was 0.45 cases per 1000 live births.²⁸

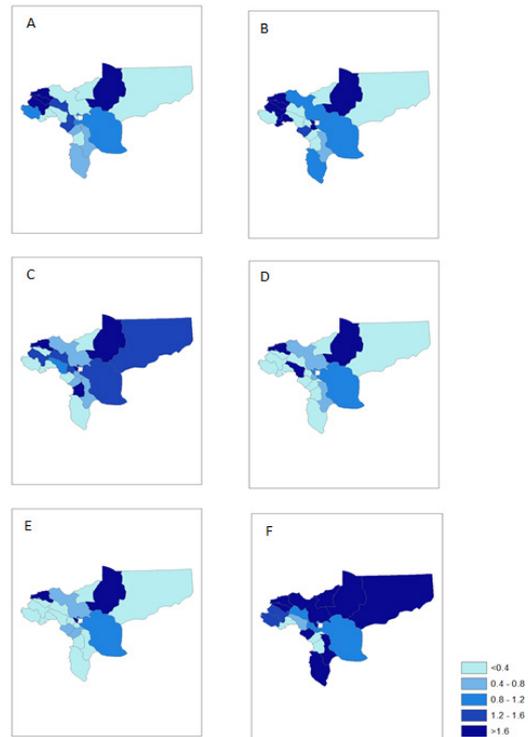


Figure 3. Spatial Distribution of Permanent Cases Hypothyroidism Incidence Rate in Isfahan Province (A:2006, B:2007, C:2008 D:2009, E:2010, F:2011).

One of the reasons for the increasing CH is the reduction of the cut-off levels of the neonatal hypothyroid screening program.²⁹ Lowering the screening thresholds compared to the initial values leads to CH diagnosis with higher sensitivity and early intervention.³⁰ As the cut-off levels for TCH is 5 in Iran, the incidence of CH has been recently reported at 1: 307.²¹ After reassessment, the incidence of permanent and transient CH was 1:581 and 1:628, respectively.²¹ In Turkey, Dill et al reported that the CH outbreak at an incidence of 1:469 in 2010.³¹

In this study, 50% of infants were diagnosed with TCH. Although the incidence of permanent and transient hypothyroidism varies in different studies, with the expansion of using screening program, an increase is observed in transient hypothyroidism. TCH prevalence is reported between 40%–54% of hypothyroidism cases^{32,33} which is consistent with our findings. Our findings regarding the high prevalence of TCH are consistent with the findings of Hashempour, Doureh, Saatsaz and Medghalchi,^{21,24,33-35} which are markedly different from that of the Isfahan Province (79.4%).^{1,3} Reports suggest that the prevalence of transient CH in most cases is 10%–15% higher than that of permanent CH.¹⁶ The reported prevalence rates are much lower in some countries, such as the USA (28%)³⁶ and Egypt (17.7%)¹⁶ compared to the rate observed in the present study.

Our findings are inconsistent with the results of other countries which have reported TCH rate at 10%–15% of hypothyroidism cases.³⁷ TCH outbreaks have been

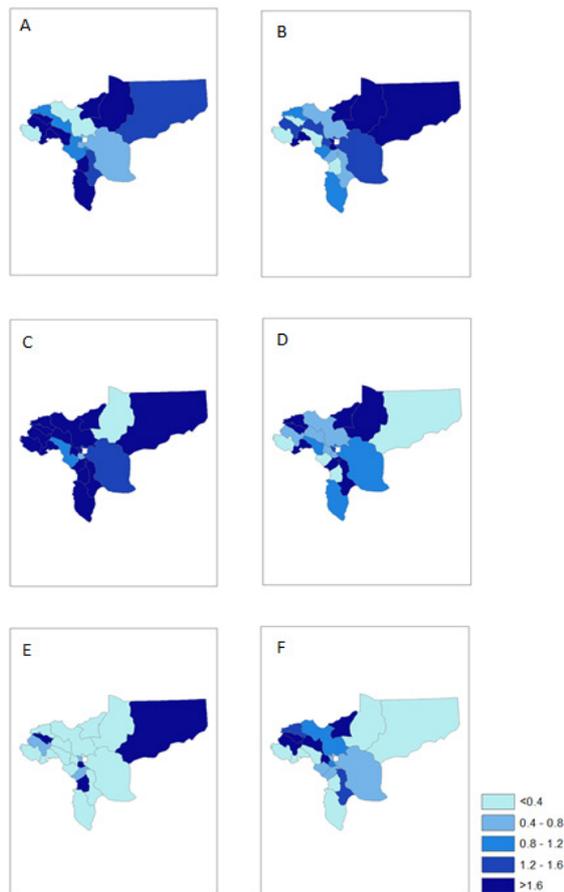


Figure 4. Spatial Distribution of Transient Cases Hypothyroidism Incidence Rate in Isfahan Province (A:2006, B:2007, C:2008, D:2009, E:2010, F:2011).

reported in different studies (from 20% to 66.5%)^{32,37-39} which are mainly due to the different definitions of TCH across studies. TCH may be due to risk factors such as deficiency or increased iodine, thyroid hormones blocker receptor antibodies, antithyroid drugs used by the mother during pregnancy, gene mutation, prematurity of newborn, and factors affecting the pituitary including drugs and untreated maternal hypothyroidism.^{1,33} Using iodine solvents in neonatal navel care and post-surgery operation care in mothers are still ongoing in both cesarean and normal delivery.⁴⁰ Some recent reports indicate iodine deficiency in parts of Iran.⁴¹ A national study also demonstrated iodine deficiency in pregnant women, despite sufficiency in the iodine status of the total population.⁴² The studies on PCH prevalence have reported its rate between 46–70%.^{32,33,43,44} In this study, 1:909 live births was diagnosed with PCH. The prevalence of PCH is reported in Babol at 1:1662, in Isfahan at 1:748, and in Mazandaran province 1:1043.^{24,33,45} However, these rates are higher than those from other regions of the world. The reported prevalence of PCH is 1:2679 in Canadian Quebec, 1:2418 in China, 1:2320 births in Italy and 1:2367 births in Argentina.^{29,46-48} This difference may be due to environmental, genetic, and immunological differences.¹⁶ One of the reasons for the increasing incidence of PCH is

the rise in the birth of premature infants.²⁷ Also, another main reason for the high CH prevalence in Iran is the high rate of consanguineous marriages.⁴⁹ According to a study conducted in Wales, using the data from 11 years of screening, the incidence rate of CH was lower in the southern compared to the northern regions, which the authors attribute to higher population density in northern regions of Wales.⁵⁰ In another study conducted in New York and the United States, differences were observed in the incidence of CH between different states, which the authors attributed to the Asian population in locations with higher incidence.⁵¹ In the results of the principal study conducted on the spatial distribution of CH in Iran, similar to the New York study, there was no specific spatial distribution for CH incidence, and the observed changes in the incidence of CH in the counties were not statistically significant.⁵² In the analysis of hot spots, in general, the hypothesis rate was tested. Its rate was high in some geographic regions and low in some other places, but the difference was not significant.⁵² Some researchers believe that geography and climatic differences can play an important role in the occurrence of CH; therefore, further studies are needed to be conducted to test this hypothesis.⁵³ Infantile hypothyroidism has several causes and most studies have been conducted to find out the causes of this disease. The occurrence of CH in Iran may be affected by environmental factors such as urbanization, and researchers have reported a higher rate of this disease in urban compared to rural children.⁵⁴ The results of our study showed that Ardestan, Khansar and Golpayegan counties had the highest incidence of CH during the study period, and unknown factors have led to the higher incidence rate of CH in these cities. Moreover, the fewest cases of neonatal hypothyroidism were reported in Fereydoun Shahr, Mobarakeh, Tiran and Krone and Shahreza counties, respectively. This difference may be due to differences in weather, living conditions or different levels of iodine in geographical areas.

The limitations of our study include failure to consider risk factors such as infant sex, infant weight, having twins, maternal morbidity, type of delivery, parental consanguinity status, birth season, etc. In addition, in the early years of beginning the screening program, lack of access to all and complete information of patients and their follow-up and indistinct type of hypothyroidism (transient, permanent) in a number of patients are other limitations of our study.

This is the first study conducted on the counties of Isfahan province, which is considered as one of the provinces with high incidence of neonatal hypothyroidism, and this is one of the strengths of our study.

In conclusion, according to the prevalence of CH in Isfahan province and covered areas and considering the role of this disease in development of mental retardation, neuropsychiatric disorders and physical illnesses, future researches are recommended to address the main causes of CH and its risk factors as an issue with high priority. These

findings need further studies to find possible factors in the etiology of CH disease in Isfahan province. In addition, regarding the spatial analysis with advanced statistical methods, we suggest adding the dimension of time to the study and performing spatial-temporal analysis, studying over a longer period of time and extending the protocol to cover other cities of Iran.

Authors' Contributions

BM collaborated in data processing; performed statistical analysis; NM involved in analysis and interpretation of data; MZ and MD helped in data collection; MS-KT conducted and managed the entire study and wrote the manuscript.

Conflict of Interest Disclosures

None.

Ethical Statement

This study was approved by ethics committee of Isfahan University of Medical Sciences with No. 293129.

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