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Spatial Analysis of Neonatal Congenital Hypothyroidism and Nitrate as an Environmental Pollutant in Isfahan Province During 2010-2013

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ABSTRACT

Background: Thyroid absorption of iodine could be encumbered by nitrate drinking water when it is transported to the fetal thyroid gland. Therefore, nitrate potentially causes congenital hypothyroidism (CH) due to thyroid dysfunction. In this study, we have not only aimed at spatial determination of CH distribution and nitrate concentration (NC) existing in drinking water, but also we intended to evaluate the probable impact of nitrate on CH incidence.

Methods: Annual average of nitrate in drinking-water as well as number of CH infants diagnosed through the screening program were applied to determine the incidence ratio of the disease for each town (from 2010 to 2013). Afterward, Arc GIS 9.3 was used to draw choropleth maps with quantile classification. Data were entered into SPSS 16.0 and Excel 2010 software. Finally, linear regression was applied for data analysis.

Results: The incidence rate of CH (considering transient and permanent cases) was about one in every 413 births. Khansar, Golpaygan, Naein, and Ardestan had the highest incidence rate of CH respectively. On the other hand, Tiran, Dehaghan, Khansar, and Fereydan had the highest level of nitrate drinking water. There was a strong relationship between the NC and incidence of CH in Khansar; however, this relationship was not significant ($P = 0.392$) in Isfahan province.

Conclusions: Since there was not a significant relationship between NC in drinking-water and incidence of CH through linear regression analysis, more studies should be implemented to confirm or refute our observations.

Keywords: Congenital hypothyroidism, Isfahan, Nitrate, spatial distribution

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INTRODUCTION

Technological progress, lifestyle changes and under consideration of human-environment interactions have jeopardized both human health and environment. Tardy tissue abnormalities and their consequent diseases might occur due to environmental factors affecting gene expression in growth periods. Clearly, iodine, which has an indispensable structural role of thyroidal hormones, is transported to thyroid through its sodium/iodide symporter (NIS). Indeed, NIS is located in locating in the cells of the placenta and thyroid gland where it also contributes to thiocyanate (SCN−), nitrate (NO3−) and perchlorate (ClO4−) transportation.[1] Not surprisingly, components inhibiting NIS activity result in hypothyroidism. Congenital hypothyroidism (CH) in newborns, which has often no or rare mild clinical symptoms, could potentially lead to mental and physical disorders unless it is efficiently diagnosed and treated. However, these medical conditions are preventable by neonatal screening.[2]

During the last two centuries, human activities have fundamentally altered the global nitrogen cycle; thus, global nitrogen has been enhanced in different areas of the earth.[3] For example, application of nitrate fertilizer, results in nitrogen-rich soil and agricultural products. Eventually, these products yield increased nitrate concentration (NC) in groundwater. This nitrate contamination is a critical jeopardy where it can affect drinking water assumed to be pumped from shallow wells.[4] Excessive intake of nitrate leads to methemoglobinemia, malignancies, as well as differences in vitamin A metabolism, and fetal developmental disabilities.[5,6] Although goitrogenic specify of nitrate is not powerful as well as other substances (such as thiocyanate and perchlorate)[7] it may result in permanent mental retardation and deafness due to thyroid malfunction.[8] Thus, determination of nitrate content in groundwater is crucial, and Institute of Standards and Industrial Research of Iran considered 50 mg nitrate/L as the maximum contaminant level (MCL) for nitrate in drinking water.[9-11] Overall levels of nitrate in drinking water are a problem that will worsen over time, and it could be due to increasing population and limited water resources.

There is some evidence from human studies that exposure to elevated nitrate levels in drinking water is associated with increased thyroid volume and increased the frequency of subclinical thyroid disorders.[4,12] NIS is expressed in human placenta, likely as a mechanism for active transport of iodide to the fetus. Recent studies found that perchlorate, thiocyanate and nitrate are actively transported across membrane barriers by NIS, raising the possibility of active transport into the fetal compartment and of potentially impaired iodide transport across the placenta. By this mechanism, ubiquitous maternal exposure to perchlorate, nitrate and thiocyanate could results in fetal exposure and impaired iodide transport. Reduced fetal iodide levels could impair fetal thyroid hormone production and possibly to reduced thyroid hormone reserves at birth,[13] so caused impair fetal brain development, permanent mental retardation, and deafness.

Because other substances could also contaminate the well water with high nitrate levels, the effect of other compounds on the thyroid cannot be excluded. Although the effect of nitrate on the functions of the thyroid gland is not known precisely, nitrate inhibits iodine from entering thyroid gland, and it does this by competing with iodine.[5]

The aim of this study was to determine geographic distribution and the incidence rate of CH as well as its relation to the spatial distribution of nitrate drinking-water in Isfahan province.

METHODS

Isfahan province, which is located in the center of Iran, covers nearly 107,000 km^2 between 30°43' and 34°27' N latitude and 49°38' and 55°32' E longitude.[14] This province is suffering from pollution due to extended industry. To elaborate, 970 units of 3700 polluting industries are located there.[15]

This was a descriptive-analytic study, which aimed to determine the relationship between neonatal CH and nitrate as an environmental pollutant. This study evaluated an annual average of drinking-water nitrate (NO3−) in 2008, 2012 and 2013. Up until 2012, the information regarding the NC in drinking water of Isfahan province was not compiled. Afterward, monthly scattered samplings in the province's towns were implemented and within 48 h, samples were delivered to the laboratory of the health center. NCs were measured by DR spectrophotometer (made in the USA) at 220 nm wavelength. The data concerned CH were collected annually (from 2010 to 2013) through screening program that targeted nearly 100% coverage of disease and its incidence rate was calculated on the base of the each town's birth. We applied the information covering from 2010 onwards, to increase its close proximity to nitrate data and to reduce the bias probability though the above-mentioned information was available from 2005. The information did not concern Kashan and Aran Bidgol districts due to lack of availability.

Monthly statistics of NC in drinking water, as well as information relating to the screening of CH and neonate population, were obtained from the database of the provincial health center. Annual incidence rate based on the total number of new cases affected with CH in total neonates born annually in every town. Choropleth maps delineating incidence rate and nitrate concentration were drawn by Arc GIS 9.3. In Arc Map, information was entered to the attribute tables of each polygon layers and then choroplth maps with Quantil classified were drawn as a raster layers in four categories. Finally, software, SPSS 16.0 and Excel 2010, were applied to analyze data using linear regression analysis.

RESULTS

From 2010 to 2013, 667 infants, out of 275,485, was diagnosed with Incidence of CH, which involved either its transient and permanent forms, during the 4 years period was 2.42/1000 births or about one in every 413 births. The results showed that CH incidence was significantly increased in 2013 [Figure 1].

Congenital hypothyroidism incidence was not equally distributed for every town of the province [Figure 2]. To elaborate, every town was assigned as one of the four groups demonstrating very high, high, moderate and low incidence of CH. Khansar, Golpaygan, Naein and Ardestan had the highest incidence of CH, whose incidences were 7.9, 5.5, 4.9 and 4.1/1000 births, respectively [Figure 3].

The average concentration of drinking-water nitrate in 2008, 2012 and 2013 did not exceed 50 mg/L, which was defined as the MCL. However the concentration of drinking-water nitrate sporadically exceeded in some water samples of the towns, whose average nitrate was highest. Classification of towns into 4 groups, according to NCs, is shown in Figure 4. Indeed, Tiran, Dehaghan, Khansar, and Fereydan had the highest average concentration of nitrate in their drinking water (36.05, 35.59, 34.37 and 29.26 mg/L, respectively [Figures 4 and 5]).

Linear regression analysis was used for examining the effect of nitrate as a risk factor on the incidence rate of CH [Figure 6]. Coefficient of determination, (R^2 = 4%) showed a weak direct relationship between these two factors. This means that 4% of the total variation in hypothyroidism can be explained by the linear relationship between nitrate and CH in Isfahan province during 2010–2013. This correlation was strongly significant in Khansar town. Regression equation between NC and incidence of CH was defined as CH = 0.039 NC + 2.265. In fact, there was an increase in the incidence of CH (0.039) when we had one unit augmentation in drinking-water nitrate. However, the above-mentioned association was not statistically significant (P = 0. 392).

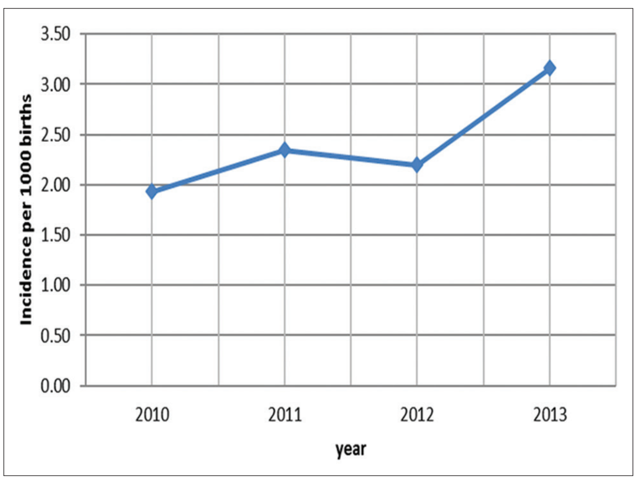

Figure 1: Trends in congenital hypothyroidism incidence per 1000 births in Isfahan province (2010–2013)

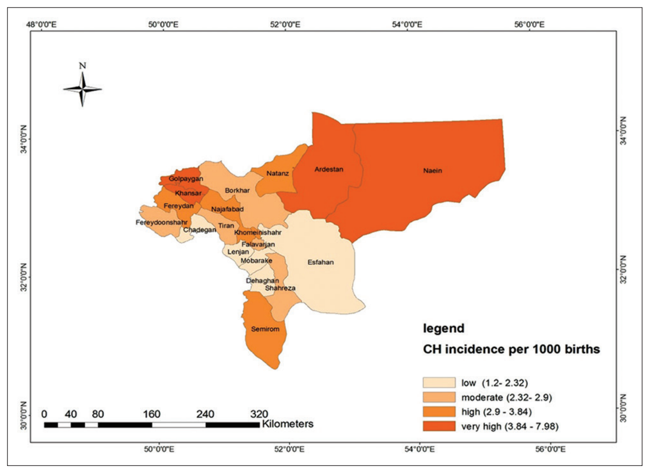

Figure 2: Spatial distribution of hypothyroidism incidence rate (considering transient and permanent cases) in Isfahan province (2010–2013)

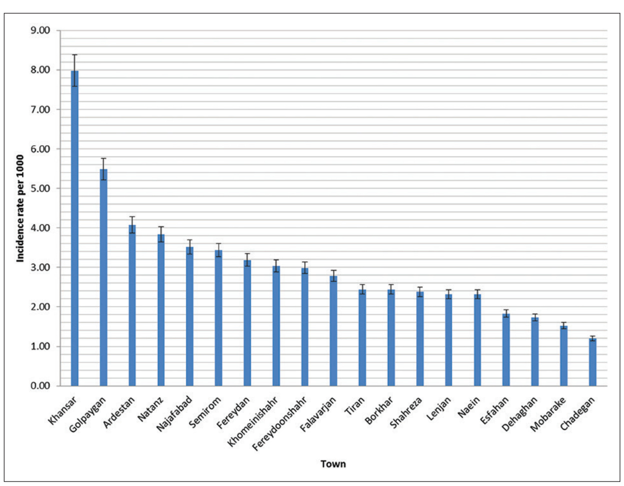

Figure 3: Hypothyroidism incidence rate (95% confidence interval) for each town (2010–2013)

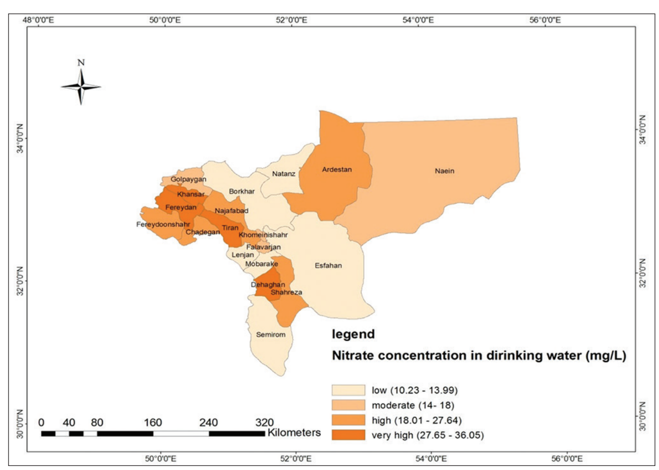

Figure 4: Spatial distribution of nitrate concentration in drinking water in Isfahan province (2008, 2011 and 2012)

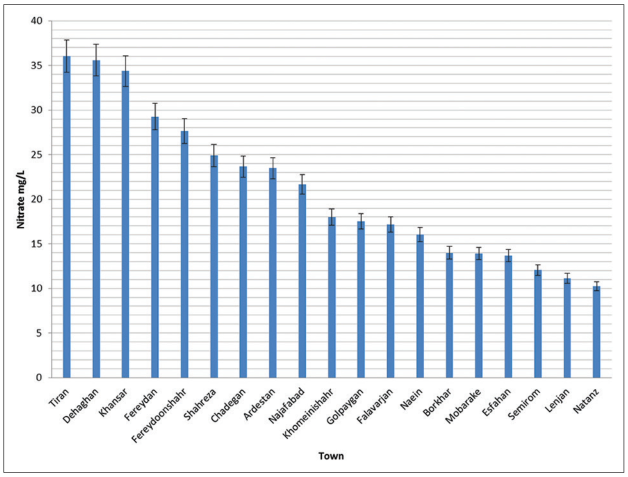

Figure 5: Nitrate concentrations in drinking water (95% confidence interval) for each town (2008, 2011, 2012)

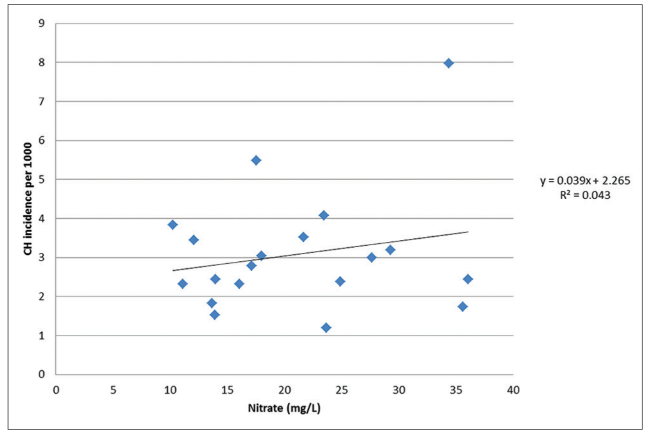

Figure 6: The relationship between nitrate concentrations in drinking water and congenital hypothyroidism incidence in Isfahan province (2010–2013)

DISCUSSION

Clearly, determination of the geographical distribution of CH and its high-risk areas is crucial to governmental policies. Appropriate disbursement for CH screening would be allocated when our geographic information system precisely determined CH distribution in our provinces and country.

The results of this study, as well as the previous reports,[16-19] showed that the incidence rate of CH, in many towns, was more than the global average. CH incidence and NC were directly (but not significantly) related. However, different studies reported that nitrate contributed less substantially toward CH in comparison with other chemical factors such as thiocyanate and perchlorate.[5,13]

While genetic, social, and environmental factors such as consanguinity and disorders affecting iodine absorption are rationally associated with CH, our common screening tests, which did not achieve appropriate specificity, potentially contribute to false or true high level of CH cases.[19-22] Besides, it seems plausible that nitrate existing in drinking water can potentially lead to CH through its competitive and inhibitory roles affecting iodine intake. Not only experimental studies, which were implemented in animal models a livestock, but also human epidemiological studies showed the possible goitrogenic and anti-thyroidal effect of nitrate in drinking-water.[23] For example, Hettche, Höring and Schiller, Sauerbrey and Andree, Höring *et al*., Höring, van Maanen *et al*., demonstrated that high NCs in drinking-water was strongly associated with goiter incidence.[12,24-28] Cao *et al*. in the US showed that thyroid hormones were deeply affected with a high level of perchlorate, thiocyanate, and nitrate existed in drinking-water.[29] Furthermore, Council on Environmental Health (2014) documented increased vulnerability of thyroid gland to certain environmental pollutants (such as nitrate, thiocyanate, and perchlorate) in the condition of iodine deficiency.[30]

However, methodological issues preclude us from definitive conclusions when some of the results completely differed.[31-40] For example, in a study which was implemented in Netherlands, thyroid function was not affected by nitrate intake.[41,42] It seems that nitrate intake is hardly likely to impact thyroid function unless the adequate range of dietary iodine (150–300 μg/day) is available. To elaborate, there was a greater likelihood of thyroid dysfunction provided a high level of nitrate intake and iodine deficiency simultaneously occurred.[26,27] However, goiter prevalence has decreased significantly after the initiation of salt iodization in Iran. nevertheless, it is still a public health problem in Isfahan.[43] According to the previous studies there was no biochemical Iodine Deficiency in neonate[44] and schoolchildren and the iodine intake of the total population was adequate so other unknown environmental factors are the cause of goiter and CH prevalence.[45] Thus, epidemiological studies might show complicated results due to iodine, thiocyanates and perchlorate differing in various regimens.

According to the map of Isfahan land use, drinking water nitrate pollution is evident in areas where agricultural activities are high, and it occur due to the use of Nitrate fertilizers and therefore entering the water. High levels of nitrate in groundwater of nonagricultural land and low population area could be due to the leaching of nitrate found in evaporitic deposits. According to available statistics, in recent years the amount of nitrate drinking water in Nain increased, maybe because of the dissolution of evaporite deposits in the region. The salt flat evaporates and salt lakes with a high concentration of dissolved salts, contain gypsum, anhydrite, rock salt and various nitrates and borates.[46]

However, to the best of our knowledge, this was the first study in Iran that evaluated nitrate impact on, as an environmental pollutant, on the incidence of CH. Spatial analysis showed that Khansar and Ardestan towns, whose NC was extremely high, had the highest incidence of CH. Nevertheless, in some areas, such as Tiran and Dehaghan, nitrate affected much less. The impact of nitrate on CH incidence rate in Isfahan province during 2010–2013 was not justified through linear regression analysis. Larger studies will be required to confirm or refute our observations.

CONCLUSIONS

Much more iodine of the dietary regimens, as well as packaging water bottles, should be recommended especially for pregnant women in areas suffering nitrate as an environmental pollutant. The impossibility of separating the transient and permanent types of disease in a recent period of study, and the low number of statistical period of nitrate measurements are main limitations of this study. Also, we did not control the concentration of perchlorate and thiocyanate drinking water and food that may cause CH prevalence. Therefore at first we recommended authorities to check the urine and milk perchlorate, thiocyanate and NC in congenitally hypothyroid neonates and their mothers and then consider the concentration of perchlorate and thiocyanate drinking water.

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