Iranian J Publ Health, Vol. 42, No. 9, Sep 2013, pp. 1016-1020

Original Article

Prevalence of Permanent Congenital Hypothyroidism in Children in Yazd, Central Iran

Mahtab ORDOOEI [1], Azar RABIEi [1], Reza SOLEIMANIZAD [2], Fatemeh MIRJALILI [3]

1. *Dept. of Pediatrics, Shahid Sadoughi University of Medical Sciences , Yazd , Iran*
2. *Dept. of Ophtalmology, Shahid Sadoughi University of Medical Sciences , Yazd , Iran*
3. *Shahid Sadoughi University of Medical Sciences , Yazd , Iran*

***Corresponding Author:** Email: dr.ordooei@yahoo.com

(Received 25 Apr 2013; accepted 09 Aug 2013)

Abstract

Background: Congenital hypothyroidism is a condition of thyroid hormone deficiency. Approximately 1 in 4000 newborn infants has a deficiency of thyroid function. The aim of this study is determination of the prevalence of permanent and transient congenital hypothyroidism (CH) in Yazd, Iran.

Methods: From May 2006 to June 2008, 35377 newborns were screened by measuring serum TSH obtained by heel prick. The neonates who had a TSH≥5mU/L were recalled for measurement of serum T4 and thyroid stimulating hormone (TSH) in venous samples. Based on the results of the secondary measurements (between days 7 and 28), neonates were considered hypothyroid if their T_4 was <6.5 mg/dl and their TSH was ≥10mIU/L. In 22 primarily diagnosed as cases of CH, treatment was discontinued at age 3 years for 4 weeks and T_4 and TSH were measured again. Permanent or transient CH was determined from the results of these tests; Patients with TSH levels ≥5 mIU/l were diagnosed with permanent CH.

Results: The incidence of congenital hypothyroidism was found to be 1:1608 with a female to male ratio of 0.69:1. In 22 patients with CH, 10 patients were diagnosed with permanent CH (45.5%) and 12 with transient hypothyroidism (54.5%). Permanent CH was associated with higher TSH levels at first measurement than transient hypothyroidism (*P*-value=0.041).

Conclusion: The rate of transient CH in our study was higher than the comparable worldwide rate, so more and larger studies are needed to find clear information about the etiologic factors of this disease.

Keywords: Neonate, Congenital hypothyroidism, Permanent hypothyroidism, Transient hypothyroidism

Introduction

Congenital hypothyroidism (CH) is one of the most common congenital endocrine disorders, affecting 1 in 3000 to 4000 newborns (1). This number varies depending on the race/ethnicity and the method of screening (2, 3). Congenital hypothyroidism results from the dysfunction of the thyroid gland and if untreated cases may lead to serious impaired mental and physical development (4). Neonatal screening programmes allow for the early detection and treatment of CH, thus preventing the mental retardation that results from the lack of thyroid hormone (1). Congenital Hypothyroidism (CH) is classified into permanent and transit forms (5). In approximately 85% of affected newborns, permanent primary congenital hypothyroidism is due to thyroid dysgenesia, which includes athyreosis, thyroid ectopia, or hypoplastic gland *in situ* and 15% due to defects in thyroid hormone biosynthesis (thyroid dyshormonogenesis) (1,4). The rare causes of permanent

hypothyroidism include resistance to thyrotropin, central hypothyroidism, developmental defects, abnormal thyroid hormone transport into the cell and thyroid hormone resistance (6,7). Transient CH may be caused by maternal or neonatal factors. Maternal factors include antithyroid medications, transplacental thyrotropin receptor blocking antibodies, exposure to iodine deficiency or excess. Neonatal factors include neonatal iodine deficiency or excess (e.g. use of iodinated disinfectants or contrast agents), congenital liver hemangiomas, very low birth weight (<1500 g) and prematurity (<37 weeks' gestation) and immaturity of thyroidal iodine organification (5,8,9). The range of incidence permanent hypothyroidism was reported between 1:357 to 1:1300 in different regions (1,4,10,11).

The aim of this study was to determine the incidence of permanent and transient CH among neonates with diagnosis of CH in Yazd screening program.

Materials and Methods

In this cross sectional descriptive study, between May 2006 and June 2008 all neonates who were screened in Yazd and had a thyroid stimulating hormone (TSH) level equal to or greater than 5mU/L were referred to the pediatric endocrinology clinic. The screening test was performed by TSH measurement on a filter paper blood spots and sampling was carried out between 3 to 7 days after birth. For these patients serum T4 and TSH levels were measured between 7-28 days after birth. With respect to the country's new protocol (based on Iranian ministry protocol) children with TSH≥10 and T4<6.5 diagnosed as CH were being treated by 10-15 μg/kg/day doses of levothyroxine. In this study children parents were requested to call for pediatric gland' proficiency clinic and then through using a questionnaire, data about gender, gestational age, birth weight, initial TSH level and level of TSH & T4 of venous blood was gathered.

Infants diagnosed with CH were followed closely for the first three years of life. They were followed every one to two months during the first year of life and every two to three months during the second and third years. In order to distinguish between permanent and transient CH, around 3rd year of follow up, levothyroxine therapy was discontinued for 4 weeks in CH cases. Then patients were reevaluated by serum TSH and T4 measurement. If the thyroid function tests showed a high TSH (TSH≥5) with low T4, the patient was diagnosed with permanent CH. Those patients with normal test results were considered to be transient cases.

This study has been approved by the Ethic Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

Statistical Analysis

Data were analyzed using SPSS version 18. A *P*-value <0.05 was considered significant.

Results

Between May 2006 and June 2008, a total of 35377 neonates were screened in Yazd and 58 neonates with an abnormal screening result were referred to the pediatric endocrinology clinic. In 22 cases, CH was diagnosed with a prevalence of 1:1608. Sex distribution of these 22 patients was 40.9% (9 cases) females and 59.1% (13cases) males (female to male ratio: 0.69:1)

The proportion of permanent and transient hypothyroidism was 45.5% (10 cases) and 54.5% (12 cases). Among 12 patients with transient CH, 6 patients had elevated TSH level and normal T4 (isolated hyperthyrotropinemia).

Next, relation between type of hypothyroidism with genus/kind, gestational age and birth weight was investigated and it was shown that there was no significant relation between type of hypothyroid and these parameters (*P* value= 0.45).

In this study Permanent CH was associated with higher TSH level at first measurement than transient hypothyroidism (*P*-value=0.041). But the mean T4 and TSH levels before starting treatment were not significantly different among patients with permanent or transient CH.

Discussion

In this study, 22 neonates had a definite diagnosis of CH that indicates an incidence of 1:1608 in Yazd, Iran. This is comparable to other studies that report an incidence of 1:1300 in the Netherlands (10), 1:1800 in Thailand(11) and 1:1456 in Fars, Iran(4). Interestingly, other studies in Iran show a higher incidence 1:357 in Isfahan (1), 1:914 in Tehran (12), 1:658 in Hamadan(13) and 1:549 in South Khorasan (14).

Hashemipour et al. relate the higher incidence to "dissimilarity between the screening methods, environmental, genetic and immunologic factors" (1). As screening methods and genetic factors in the present study are the same as in other studies in Iran, environmental factors may play a more prominent role in the incidence and prevalence of CH.

This finding is similar to that of other authors in Iran such as Hashemipour et al. that report 59.8% permanent and 40.2% transient CH (1) or Karamizadeh et al. that report 53.6% permanent and 46.4% transient CH (4). Some other studies report a reverse ratio; Gaudino et al. found 38% and 62% of 79 patients with CH as transient and permanent CH (15). In the study by Ordookhani et al. of 35 neonates with primary congenital hypothyroidism, 25 (71.4%) had permanent CH, six (7%) had transient CH, and four cases were unclassified (16). In a study from Saudi Arabia, only two of 24 neonates with CH had transient CH (17). It is generally accepted that 5-10% of primary CH patients are diagnosed with the transient type (18,19).

Higher rates of transient CH may be due to iodine deficiency, iodine overload, transplacental passage of thyrotropin (TSH) receptor blocking autoantibodies, elevated thyroid autoantibodies, anti-thyroid drug ingestion or the use of iodine-containing topical antiseptics, maternal consumption of goitrogens and/or thyroid affecting medications, neonatal very low birth weight (<1500 g) and prematurity (<37 weeks' gestation) and immaturity of thyroidal iodine organification (8, 20-22).

A recent study by Ordookhani et al. has reported that elevated urine iodine concentration was the most frequent finding in newborns with transient CH (23).

Moreover, in a study conducted by Hashemipour et al. it was recommended that considering iodine shortcoming in Esfahan and the lack of localized antiseptic drugs usage in hospitals, more studies should be conducted about autoantibodies and extra amount of iodine limit with respect to iodine -included supplements (1).

In a study from Australia, 14 of 24 transient cases were due to excessive intake of iodine. In two, this was due to maternal ingestion of iodide during pregnancy and in 12 the babies received large amounts of topical iodine antiseptic. The large number of cases due to the topical application of iodine antiseptic emphasizes the need for caution when using this substance in neonates (24).

The limitation of our study was that we did not evaluate causes of transient CH, so further investigations are needed to understand the causes behind higher rates of transient CH.

In this study, based on current country's protocol (TSH≥10) the occurrence of permanent and transient CH amounted as 1:3537 and 1:2948 births respectively that is almost similar to permanent CH world's prevalence. However, based on the country's previous protocol (TSH≥5) the occurrence of permanent and transient CH amounted as 1/2721 and 1/1219 births respectively that may conclude that most of the children with 5≤TSH<10 were transient CH; however, they need exact follow ups; hence in a study conducted by Dr.Karamizade et al. it was recommended that children with transient CH must undergo longer follow-ups, because in their study those patient with normal TSH, about one month after drug cut-off, encountered with TSH elevation after 4-5 months resulted in permanent CH diagnosis (4).

In addition in our study, 3 children with TSH=5-10 had permanent CH; therefore, we recommend that children with TSH=5-10, regarding that they do not included in the country's protocol, they should be followed up regularly and their clinical symptoms of hypothyroid be seriously considered

and in case of clinical suspension thyroid's function test should be considered or at least their test be repeated in incoming months.

A noticeable point is patients with high TSH and normal T4; Muge Tamam et al. reported 17% of 182 patients as "Isolated Hyperthyrotropinemia", that were neither transient nor permanent cases of CH. They recommend that these patients can be followed without hormone therapy (25). In the study by Karamizade et al. 35% of transient cases and 17% of total CH cases had same laboratory features (4). In our study 50% of transient cases had same laboratory features also. In this study and most probably in other studies in Iran these cases were labeled as transient hypothyroidism.

Therefore we believe that this can be a major factor for a higher rate of transient CH in our study.

In our study, the rate of prematurity was not significantly different between transient and permanent CH, whereas according to some reports prematurity is a risk factor for transient CH (15). In our study, the mean TSH level before starting treatment was not significantly different among patients with permanent or transient CH, whereas according to some reports the mean TSH levels before treatment were significantly higher in the patients with permanent CH than in those with transient CH (1, 4, 26).

But in our study Permanent CH was associated with higher TSH level at first measurement than transient CH. It was concluded from this finding that the firs TSH level may has a predictive role for identifying permanent forms of CH from the transient forms.

Conclusion

In this study transient CH has a significantly higher rate than other similar studies, so more and larger studies are needed to find clear information about the etiologic factors of this disease.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

Acknowledgment

We acknowledge the contribution of Dr. Mizraei, Dr. Jafarizade and Dr. Evazinejad in preparing this manuscript. The authors declare that there is no conflict of interest.

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