



Effectiveness of neonatal screening for congenital hypothyroidism

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Abstract

Introduction: Congenital hypothyroidism (CH) is the most common preventable cause of mental retardation. Newborn screening program considerably increases probability of CH diagnosis and treatment.

Objectives: We aimed to investigate the efficacy of running CH screening program to maintain normal IQ and physical growth of hypothyroid children in Semnan city.

Patients and Methods: This study was performed on children with definite CH who were treated and followed up in Semnan health centers. Around 41 children born within 2008-2013 (minimum three years of age) participated. Respective weight and height for age were measured. The Z-scores were calculated based on the WHO-Anthro-Plus Software. Intelligence Quotient (IQ) was measured with Wechsler Intelligence Scale for children-revised (WISC-R). Data analyzed with one-tailed *t* test compared with age and gender-matched group.

Results: The mean IQ Score in our study group was 90.09 (1.73) with no significant difference compared to healthy counterparts ($P > 0.05$). Z-score for weight and height was -0.46 and -0.45 prospectively and was not significantly different from normal children.

Conclusion: Newborn screening program for CH has been effective in preventing mental retardation and growth failure.

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Introduction

The worldwide incidence of congenital hypothyroidism (CH) was reported 1:1000-4000 live births (1-5). Rate of CH was about seven times higher in Iran based on the national report (6).

The incidence of hypothyroidism varies in countries (2,3,7-9). The trend of the disease in a particular region also varies with time (2,7,10). These differences might be explained by increased survival of preterm- very low birth weight infants (11), several screening guidelines and cut off point for definite diagnosis (12,13), dietary iodine deficiency (4,10,13). Other possible mechanisms were transient hypothyroidism following overuse of iodide-containing solution (1,14), ethnic, racial, tribal differences in thyroid genesis and function (15-17).

Besides, most researches concentrating on investigating the efficacy of CH screening systems had retrospective design. Therefore, their results affected by confounding factors

Key point

Congenital hypothyroidism is the most common preventable cause of mental retardation. "Newborn screening program for congenital hypothyroidism" is an effective program in preventing mental retardation based on IQ score (WISC-R) and growth failure according to Z-score of anthropometric indexes in followed up children.

that could not be controlled. Altogether, estimation of CH prevalence based on such studies could be biased (10,18). Alongside this, a remarkable proportion of the world lack a screening program (4,5,18) or have a poor newborn screening (NBS) coverage or imprecise health information system (4,19).

There are some pieces of evidence about worldwide rising trend of CH that is too much to justify only by increasing the accuracy and coverage of the NBS program (1,7). Several studies have illustrated higher prevalence of CH in Iran in comparison to the world (3,6,8,10).

Although the higher ratio of transient hypothyroidism due to iodine deficiency (17,19) and consanguineous parents (4,20) partly explained incidence rate in our country, timely diagnosis and treatment even in transient cases are mandatory to prevent growth and neurodevelopmental defects. If thyroid hormone deficiency remains unrecognized and untreated for more than 2 weeks after birth, can lead to permanent mental retardation, higher risk of other congenital anomalies, metabolic disruptions and consequently severe social and economic burden on the family and the society (5,6,18,21,22).

The main indicator in studying the effectiveness of NBS for CH is maintaining normal IQ score, preventing borderline IQ score or in other words, preserved IQ score in time interval (6,21,23). Additionally, physical growth of CH cases remained within normal age and sex matched healthy children (4,23).

Objectives

Therefore, effectiveness of NBS program for CH infants as a priority has been investigated in different levels and areas in time trend as a part of the health system evaluation (18,21,24). We aimed to study the efficacy of running CH screening program to maintain normal IQ and physical growth CH live births in Semnan city.

Patients and Methods

Study design

CH screening Program has been presented worldwide in 1970. Pilot study began in 2004 in our country and 1 year later integrated into national health care system. It reached rapidly to 97% coverage in both urban and rural regions. This program began in Semnan province in 2007 and is continuing. All neonates (3-5 days of age) have guided to referral screening laboratory. Capillary blood sample is to be taken by heel prick method on filter paper. Infants who have been diagnosed as hypothyroidism after confirmation of screen positive cases by venous blood sample visited by focal point physician and then followed up through health centers in parallel to routine health care.

Optimal treatment is a prerequisite for preventing mental retardation and growth failure. Follow up visit up to 3 years of age could differentiate transient hypothyroidism cases and lead to withdrawal of treatment. Drug therapy of permanent cases persists lifelong.

Wechsler intelligence score for children (WISC) was developed in the 1930s and was first coherently used by researchers in 1949 (25). In 1972, the initial revision of the test and its questions was carried out and then translated and evaluated by Iranian researchers in a package in 1992, revised thereafter and is still used in Iran for children. WISC could be performed from minimum 3 years of age, for preschooler (6-19) and adults (26). Besides, WISC also has been used as health screening for readiness to enter primary school at six years of age. Therefore, applying the same tool facilitates longitudinal studies.

Verbal and functional component of test have been summarized to final IQ score. WISC final score has been classified as average (90-109), low average (80-89), borderline (70-79). We selected 90 as minimum normal and ≤ 70 as borderline or pathologic IQ. Validity and reliability of Wechsler test in age group of 3 to 6 years (26) and above six years (27) was acceptable.

This study was on children diagnosed with CH by national NBS. Among treated cases, 41 children over three years of age who were able to participate in WISC were selected. Families were contacted for interview and IQ test through city health centers. The interview with parents and IQ test from children were done after parent's informed consent. Patients with concomitant genetic disease, ADHD, autism and maternal alcoholism were excluded from the study.

The study checklist was filled in through interview with parents and child's documents in health center. It included demographic data, anthropometric indexes at birth, and some probable risk factors such as consanguine families, type of delivery. Meanwhile, a test expert psychologist has achieved the child's intelligence test based on appointment in the same center. The psychologist tried building trust and familiarizing children with the test environment. Wechsler test lasted for 75 minutes and was measured with a chronometer.

Baby height and weight were measured with a digital scale (precision 100 g) and non-flexible plastic meter tape (precision 0.5 cm), which was the same for all children. Anthropometric indices were analyzed using WHO Anthro Software for up to five years of age and WHO Anthro-plus specific for 6-19 years of age (28).

Z-score for anthropometric indexes, weight for age, height for age, weight for height and BMI present standard deviation from mean children adjusted for age and gender and due to sampling method could be representative of growth rate of children. Comparing growth curve standard based on Z-score is more precise than percentile, because Z-score measures a distance, meanwhile percentile presents a cut off and could be misleading and inappropriate for measuring growth rate (29).

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The institutional ethical committee at Semnan University of Medical Sciences approved all study protocols (IR.SEMUMS.REC.1394.226). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from M.D thesis of Behrouz Shayestefard at this university (Thesis#1143). Objectives of the study were explained to the parents. They were volunteered to participate in the study by signing informed consent. The participants could leave the project at any time without any interruption in their children's treatment plan.

Data analysis

The data was analyzed by SPSS software version 22. Relationship between variables was calculated by one-sample *t* test, chi-square (χ^2 test), Fisher's exact test. The significance level was considered 5%.

Results

Table 1 demonstrates the number of infants born each year 2008-2013 and prevalence of hypothyroidism during these years.

The prevalence of hypothyroidism in these years in our country was 33 in contrast to 46.3 in 10 000 live births in Semnan city. Coverage of screening program was 100% from 2008 up to 2013. We could find about half of them and most of them (45%) participated in this study.

Table 2 shows the general characteristics of study group. Of 41 confirmed congenital hypothyroid cases, 24 were female (58.5%), 27 (65.9%) delivered by cesarean section and 15 were offspring of consanguineous marriage.

Average time interval between screening and definite diagnosis and treatment was about 22 days. About 66% (27 parents) were highly and 29% (12 families) moderately satisfied with screening program and follow-up care. Less than 5% of caregivers were disappointed with the program.

Treatment was stopped in five patients based on physician order and 36 patients were under therapy at the time of survey.

Mean birth weight and height of study group was 2936 gram and 47 cm respectively. Mean age, height and weight at the time of study were duly 63.3 months, 108.7 cm and 18 kg.

Mean IQ Score in our study group was 90.09 (1.73). The mean IQ score of diagnosed cases was not significantly different compared to healthy counterparts ($P > 0.05$). None of studied patients had borderline IQ score (≤ 70). Mean of annual saved IQ score was about 118 (in total 824).

Anthropometric indices Z-score was computed by Anthro and Anthroplus software (28). **Table 3** presents Z-scores (standard deviation of anthropometric indices) for weight and height for age and weight to height and body mass index (BMI) at birth and the age of follow-up study.

The last column shows difference between Z-score of all calculated indexes by subtracting birth Z-score from follow-up Z-score of cases. According to this column, Z-score of all indexes were increased in follow-up and these differences were statistically significant in all of the indexes above ($P < 0.05$) except for height for age. Height for age Z-score increment at follow up was the least and not significant overall and based on individual sex group.

Weight for height Z-score is more reliable index of growth rate than BMI in children especially under 5 years of age. A new Z-score difference index was extracted from Z-score differences of BMI and weight for height. We substituted BMI by weight for height Z-score difference when both of them exist (Mean 0.66, SD 1.5). *P* value of this new index was significant ($P = 0.008$) and remained significant in girls when the data analyzed based on gender ($P = 0.027$). This index was even significantly higher in children with healthy parents compared to the hypothyroid group ($P = 0.030$).

Discussion

In this study, we evaluated the efficacy of CH screening program in Semnan city using IQ scores (WISC) and anthropometric indexes of identified and treated patients.

The screening program planning began in 2003 and after a pilot study was integrated into our health care system in 2005 (3). Screening was running in Semnan province since 2007 and its coverage reached 100% only after several months. The implementation of screening program based on global standards, maintaining social responsibilities for

Table 1. The birth rate and prevalence of congenital hypothyroidism in Semnan city, 2008-2013

	2008	2009	2010	2011	2012	2013	Total
Number of CH infants identified	20	14	21	15	8	13	91
Number of participants in our survey	1	7	6	11	3	13	41
Live birth rate	3126	3056	3257	3347	3057	3796	19639
Prevalence of CH per 10000 birth	64	46	64.5	45	26.2	34.2	46.3
1 CH per no of live births	156	218	155	223	382	292	216

CH; congenital hypothyroid.

Table 2. General characteristics of study group (children with positive test for congenital hypothyroidism)

Variable	No. (%)	Mean (SD)
Gender	Male: 17 (41.5)	Female: 24 (58.5)
Birth weight-height	2936 (347) g	48 (2.4) cm
Type of delivery	Vaginal: 14 (34.1)	Cesarean: 27 (69.5)
Consanguineous family	Yes: 15 (36.6)	No: 26 (63.4)
Hypothyroidism in mother	Yes: 17 (41.5)	No: 24 (58.5)
Child treatment continued	Yes: 36 (87.8)	No: 5 (12.2)

Table 3. Z-score of anthropometric indexes birth – follow up and Z-score difference

Z-score	Birth Mean (SD)	Follow-up Mean (SD)	Z-score Difference Mean (SD)
Weight for age	-0.81 (0.8)	-0.46 (0.7)	0.35 (0.9) ^a
Height for age	-0.56 (1.3)	-0.45 (0.7)	0.08 (1.4)
Weight for height	-0.52 (1.7)	-0.05 (0.6)	1.33 (1.7) ^b
Body mass index	-0.80 (1.3)	-0.21 (0.8)	0.61 (1.4) ^c

^a P value = 0.025, ^b P value = 0.008, ^c P value = 0.010

its monitoring and evaluation is a serious health priority to prevent a major cause of neurodevelopmental disorders. Besides, blood samples and data could be used in other researches. Accordingly, our research is also done to evaluate the performance of the health system to prevent one of the most important causes of preventable mental retardation. Performance of CH screening system should be proven in all areas and in one area over time.

In the present research, the prevalence of the CH was 1: 216 live births and about 2.1 higher than country level (1: 462) (23). CH incidence fluctuated between 1: 155 to 1: 382 between 2008 and 2013 (2, 6, 8, 30). The ratio of CH began from 1: 184 in Mashhad (17), 1:370 in Isfahan (10) to 1: 914 in Tehran (3) in the last two decades. Regardless of how the differences in statistics between cities and in time trend can be argued, the increased prevalence of hypothyroidism in Iran indicates the importance of a global screening program with a comprehensive and standardized evaluation system.

A review of the results of previous studies shows that incidence of CH in different parts of the world has not been homogenous (4). The prevalence of CH in EMRO region was 1:2934 live births in Turkey (9), 1:3292 in Saudi Arabia (20). In the eastern region of Asia was 1:1136 in Japan (31), 1:1992 in Taiwan (19), and 1:764 in Mongolia (32). In Europe, from 1:1800 live births in Greek Cypriots (33) to 1:1970 in Italy (1).

Increasing worldwide prevalence of CH could be explained partly by change in the coverage of program (1,13,22,34), methodology (4,11), instrumentation and protocols (TSH lower cut off) (1,14), pregnancies outcome, birth demography (8,35), ethnicity (5,7).

Higher prevalence of screening positive neonates in our city in contrast to country level (6,8) could be explained by complete coverage of program and higher prevalence of transient cases due to factors that affecting the trend (2,10,17,36) such as iodine deficiency (16), geographic area (10,17), ethnicity (15,31,34).

Female predominance in our study (1.4 to 1) was in accordance with previous studies (19,34) and opposite to first report by Zeinalzadeh and Talebi from East-Azerbaijan, Iran (36). Interpretation of gender differences in our study with contrasting past studies could not be accurate as our sample size was too small.

Withdrawal of treatment occurred in 5 cases (12.2%). Based on a review, transient hypothyroidism occurred

in 17% to 40% of screened cases later in childhood. Although the majority of the transient hypothyroidism cases occurred in third year of life, diagnosis of some cases delayed until seven years of age or more (14). Both transient and permanent cases need to be treated but the underlying cause should be investigated carefully. Comprehensive report including medical geography in parallel to precise case records required to evaluate national and local intellectual and developmental disabilities program.

Several studies in Iran (3,6,37) and other countries have confirmed efficacy of CH screening program based on average IQ score in follow-up of cases. IQ score of diagnosed cases was not significantly different from minimum IQ score range of normal children (IQ=90-110) as other studies in our country (6,23,37) and worldwide (18,24,31).

Some studies in Iran (21, 36) and other countries (4, 24, 38) have shown lower IQ scores in follow up after 6-12 years but none of them had borderline IQ score (IQ ≤70) based on WISC-R in accordance to our study.

In the present study, saved IQ scores per defined and treated case by screening program were estimated at 20. Yarahmadi et al have shown even more saved individual IQ Score (36 scores) from national survey in 2006-2007 (6). Main outcome of CH screening program is normal neurodevelopmental outcome comparing age and sex matched healthy group. Lastly, it could be implied on effectiveness of this screening program on promotion of cognitive and neurodevelopmental health outcomes of congenital hypothyroid cases.

Similar to other studies (6, 21), not only mental retardation but also physical growth failure could be prevented by early screening and proper treatment of cases both with transient or permanent hypothyroidism. WHO's growth standards are used for children growth's monitoring. Standard deviations of anthropometric indices (Z-score) of subject group were significantly higher than mean weight - BMI for ages and weight for height standards Z-scores.

In contrast, height for age Z-score changes in follow-up were not statistically meaningful as in other researches. Some studies concluded suboptimal or failed height growth due to time to onset and dose of treatment (2,37)

There were some limitations in this study such as changing the contact address of some families, loss to follow up and lacking of health center documents, as well

as the difficulty in communicating with children.

Conclusion

Efficacy of the “Newborn screening program for CH” has been confirmed in preventing mental retardation based on IQ score (WISC-R) and growth failure according to Z-score of anthropometric indexes in followed up children.

Limitations of the study

The most important limitation in this study was the change of patients’ addresses and also the defects in the records, which were partially eliminated by finding the new addresses of the patients and also supplementary interviews.

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Authors’ contribution

EG and MA were the principal investigators of the study. EG, NSK and MA were included in preparing the concept and design. BSH collected the data. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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