



A Success Story: Review of the Implementation and Achievements of the National Newborn Screening Program for Congenital Hypothyroidism in Iran

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Abstract

Context: Today, newborn screening for congenital hypothyroidism (CH) as one of the significant achievements in preventive medicine is integrated into the health systems of many countries worldwide. The national newborn screening for early identification of CH disorder in Iran was established in 2004. The purpose of this study was to review the national newborn screening for CH and its achievements in Iran.

Evidence Acquisition: In this study, we reviewed the structures, processes, main indicators, and achievements during the 15 years of implementing the national neonatal screening program for the diagnosis and treatment of CH in Iran.

Results: Primary TSH measurement with backup thyroxine (T4) determination in infants with high TSH levels was used as the screening strategy in Iran. The coverage of this screening program was higher than 98%. By the end of 2017, 1,501,624 neonates were screened, among which 40,773 were diagnosed with CH and treated based on the national guidelines. The average incidence rate of CH during these years was approximately 2.6:1,000 live births.

Conclusions: The performance of the newborn screening program for congenital hypothyroidism in Iran is favorable, with over a 95% coverage rate. Due to the high recall rate and incidence rate of CH, it is essential to monitor the screening program in the country and also to conduct further studies to determine the main risk factors for the high recall rate and incidence of this congenital error.

Keywords: Neonates, Screening, Congenital Hypothyroidism, Iran

1. Context

More than 60 years have passed from the establishment of neonatal screening programs in the world, especially in developed countries (1). Neonatal screening can be used as a prevention activity in various areas such as endocrine, metabolic, genetic, hematologic, and infectious diseases (2). With the launching of the first neonatal screening program in the 1960s, a new window was opened for improving the health of infants and children (3).

Congenital hypothyroidism (CH) is one of the common treatable causes of mental retardation, and its delayed diagnosis can lead to the most severe outcomes, especially mental retardation (4, 5). Based on the nature of the disease, CH is considered as one of the target diseases, which requires screening worldwide (6). Failure in the treatment of CH imposes many economic costs on individuals, fam-

ilies, and society. However, with prompt diagnosis, treatment interventions are straightforward, inexpensive, and effective in preventing complications and consequences caused by the disease (7).

According to existing evidence, the first screening program for CH was established in April 1974, in Quebec, Canada (8, 9). Today, newborn screening for CH as one of the significant achievements in preventive medicine is integrated into the health systems of many countries around the world (10, 11). The national newborn screening for early identification of CH disorder in Iran was established in 2004. The purpose of this study was to review the national newborn screening program for CH along with its structures, process, and achievements, in Iran.

2. Evidence Acquisition

This study was designed to evaluate the structures, processes, main indicators, and achievements during the 15 years of implementing the national neonatal screening program for the diagnosis and treatment of CH in Iran. In this study, before discussing the success of the program, we introduced the national newborn screening for CH, and listed all the main steps for implementing the program in Iran.

To conduct the study, all documentations related to implementing the program, including the screening, treatment, and follow-up protocols at different levels as well as the surveillance system data from the beginning of the program, were used to assess the achievements and success rate of the program's implementation. In addition to calculating the annual incidence rate of CH, the average incidence rate during all the years of conducting the program was also obtained using the surveillance data of CH registered at the provincial and national level. We utilized ArcGIS software to better illustrate the epidemiological picture of CH incidence in Iran's provinces during the 15 years of implementing the program.

3. Results

The main objective of this study was to introduce the national newborn screening program to identify CH and reflect its achievements. The results of the study are presented in the following sections as several steps, including the year of running the program, objective, screening test and process, treatment, data registration, and main achievements.

3.1. Year of Running the Program

Although pilot studies of CH screening have been carried out since 2004 in three provinces of Iran, including Tehran, Isfahan, and Bushehr, the screening of newborn babies was integrated into the national health system on September 23, 2005.

3.2. Objective

The main objectives of this program were early detection and timely treatment of children with neonatal hypothyroidism in Iran. Accordingly, the program's guidelines of CH surveillance were designed for different levels of the health system.

3.3. Primary Screening Test

There are three screening strategies for the detection of CH: (1) primary T4 measurement with backup TSH assessment in infants with low T4 levels; (2) primary TSH measurement with backup thyroxine (T4) determination in infants with high TSH levels, and (3) measurement of both T4 and TSH levels in primary screening. The national newborn screening program in Iran utilized the primary TSH measurement method with backup thyroxine (T4) determination in infants with high TSH levels as the screening strategy. There exists scientific evidence regarding the effectiveness of primary TSH measurement with backup T4 assessment on such infants.

3.4. Screening Process

The CH screening program is carried out in several successive steps. In the first step, all pregnant women are taught face-to-face by healthcare personnel about the importance and necessity of screening infants for early CH diagnosis within 3 - 5 days after birth. In the next step, and after sensitizing the mothers, screening for infants is performed by measuring TSH in the peripheral blood. For this purpose, four drops of blood are taken from the baby's heel. After placing the blood drops on an S & S 903 filter paper, the sample is sent to the selected laboratory for analysis. The third step is to measure the TSH concentration in the laboratory. In the fourth step, babies whose TSH values are higher than normal are invited, and their thyroid hormones, including T4 and TSH, are measured intravenously. Some cases, such as neonates with hospitalization history after birth, preterm newborns, neonates with low birth weight (weight < 2500 g), twins or more, and neonates with a history of blood transfusion, will be re-sampled using heel prick sampling in the second week, even if their initial TSH value is normal. For infants detected as CH after sampling venous blood and evaluating the TSH and T4 values, treatment with levothyroxine is initiated immediately (Figure 1).

3.5. Treatment and Follow-Up

The main objectives of the national newborn screening program for CH in Iran include early diagnosis and replacement of thyroid hormone. Following a positive screening test (TSH), and as confirmed by additional tests, the treatment starts immediately for infants identified as having CH. The treatment is conducted and supervised in each city by focal point specialists. The drug used to treat patients is an oral levothyroxine tablet. The recommended dose for the start of the treatment is 10 to 15 $\mu\text{g}/\text{kg}/\text{day}$ based on the national guidelines. For each identified CH case, follow-up and care are provided at least until the age of three. In

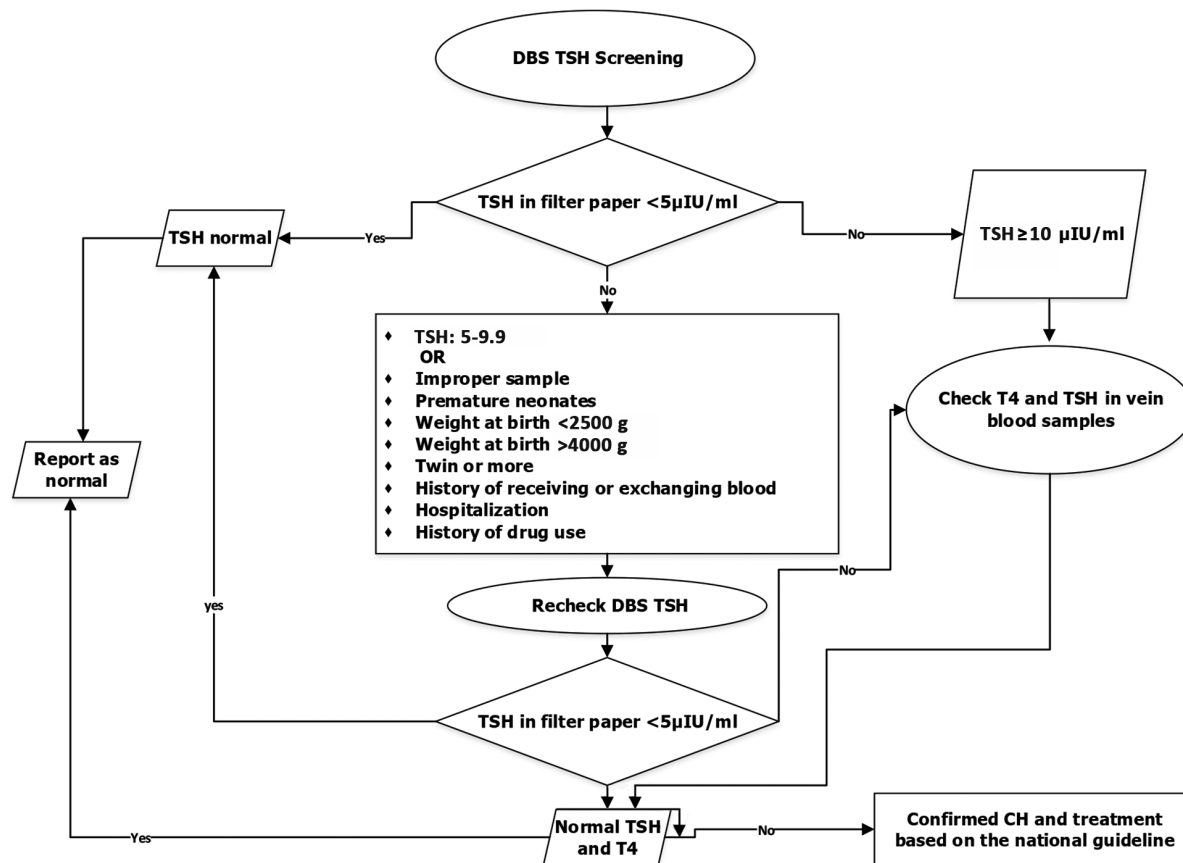


Figure 1. The flow diagram of CH screening in Iran. Abbreviations: DBS, dried blood spot; TSH, thyrotropin; T4, thyroxine; CH, congenital hypothyroidism.

each follow-up session, patients are visited by the physician, and their hormonal tests are checked. According to the national guidelines, the schedule for these follow-ups is as follows:

- A) Two and four weeks after the start of the treatment
- B) Every two months until the age of six months
- C) Every three months between the age of six and 36 months
- D) Every six months after the age of 36 months (for permanent cases)

3.6. Data Registration

The process of registering the CH data, including the number of newborns, screened neonates, and children diagnosed with CH at all levels of the national health system and in all the districts of the country, was completed in 2006.

3.7. Achievements

From the beginning of this screening program in Iran (2005) until now, millions of newborns have been screened, and thousands of them have been identified and treated as CH cases. Remarkably, the coverage of the national newborn screening program for CH is more than 98%. The recall rate of newborns based on high TSH in primary evaluation has ranged from 3.2% to 7.3% in different districts of the country. According to the national surveillance system, by the end of 2017, 1,501,624 neonates were screened, and 40,773 of them were diagnosed and treated as CH cases. The average incidence rate of CH, both transient and permanent forms, has been approximately 2.6:1,000 live births during these years. The number of screened newborns, infants diagnosed with CH, and the incidence rate of the disease (transient and permanent CH) in each year between 2006 - 2017 are summarized in [Table 1](#). According to [Table 1](#), an increased incidence rate in CH has been observed over time, so that the incidence rate from 2006 (2.2:1,000) to 2017 (3.1:1,000) indicated an increasing

trend. It appears that the change in the initial TSH value cutoff from 10 mIU/L in the first years of screening to 5 mIU/L during the recent years has resulted in reduced false negatives, which might be the reason for the gradual increase of the CH incidence rate in Iran. It should be noted that the incidence rate of CH differs in all the districts of Iran, ranging from 1.6 to 4.4 per 1,000 live births (Figure 2).

Table 1. Results of the National Neonatal Screening Program for CH in Iran During 2006 - 2017

Year	Number of Neonates Screened	Number of Neonates Diagnosed with CH	Incidence (in 1000 Screened Neonates)
2006	612786	1352	2.2
2007	1017080	2472	2.4
2008	1156169	2819	2.4
2009	1237428	3082	2.5
2010	1281939	2967	2.3
2011	1338244	2948	2.2
2012	1380751	3496	2.5
2013	1445696	3859	2.7
2014	1530393	4106	2.7
2015	1570067	4602	2.9
2016	1471546	4365	3.0
2017	1501624	4705	3.1
Total	15543723	40773	2.6

Abbreviation: CH, congenital hypothyroidism.

4. Challenging Issues

Despite the fact that Iran has demonstrated great success in implementing the national newborn screening program for CH, the high incidence rate of CH, especially in some districts of Iran, is challenging, which necessitates further research efforts in the field. It is clear that the rise in the incidence rate of CH could not be attributed solely to demographic factors, and it can be influenced by genetic (the high consanguinity rate in Iran) and environmental factors such as iodine deficiency or excess.

Another challenging issue, which puts a great burden on families and health systems, is the false-positive rate in screening results caused by changes made in the screening algorithm, primarily by a decrease of the TSH cutoff in the national guidelines of CH surveillance during recent years and subsequent increase in the recall rate, one of the program indicators. It should be noted that there is no strong scientific evidence to justify this conclusion. Accordingly, in one study conducted in Iran, it was concluded that we

had an appropriate screening outcome if the cutoff point for recall changed to 7.5 mIU/L (12). Therefore, one of the most important challenges of the newborn screening program for CH in the world is to determine the suitable cutoff value for screening tests to the level that could maintain the highest sensitivity. The reason is the ability to find all cases while considering test specificity and a positive predictive value. Modifying cutoff values changes the diagnostic sensitivity of the surveillance system as well as the number of false negatives (13, 14). In the national newborn screening program for CH in Iran, the initial cutoff value for the TSH test is set at 5 mIU/L. Large cohort studies are required to find the specificity and sensitivity of different TSH screening cutoff points to find the best cutoff to decrease the recall rate. Nevertheless, other causes of the high recall rate should not be ignored in different regions (15).

Despite the great success of the national screening program in identifying and treating children with neonatal hypothyroidism, some critical aspects of the CH surveillance system have not been evaluated yet. Because of the necessity of prompt identification of patients and timely initiation of treatment, attention to the time of each process (the timeliness indicator) is one of the most critical aspects of the CH surveillance system, which needs to be reviewed (16, 17). Although in a retrospective cohort study in Iran in 2011, all the program indicators were nationally evaluated and yielded, and they were highly suitable results regarding timeliness indicators, e.g., time of screening and time of treatment initiation (18).

Despite having a detailed national protocol for the implementation of newborn screening, there are still some points that need to be incorporated into the national protocol based on new and valid scientific evidence. Having a specific strategy for additional screening at 4 to 6 weeks of age in case of severe prematurity, highly low birth weight (VLBW), and critically ill neonates are important points that should be considered during the revise of the national protocols. An exact strategy was utilized for a second screening at ~2 weeks of age in all preterm or low-birth weight (LBW) newborns (9), and also, in neonates admitted to the neonatal intensive care unit. Additionally, we have a specified strategy when venous TSH is between six and 20 mIU/L in a healthy baby with free T₄ (FT₄) within the normal limits for age, where the optimum management is still debated. In fact, the decision to start the treatment with L-T₄ depends on multiple factors, such as the patient's age, duration of the thyroid dysfunction, the trend of TSH values, etiology, presence of syndromes and/or other pathologies, and parents' choice (14, 19).

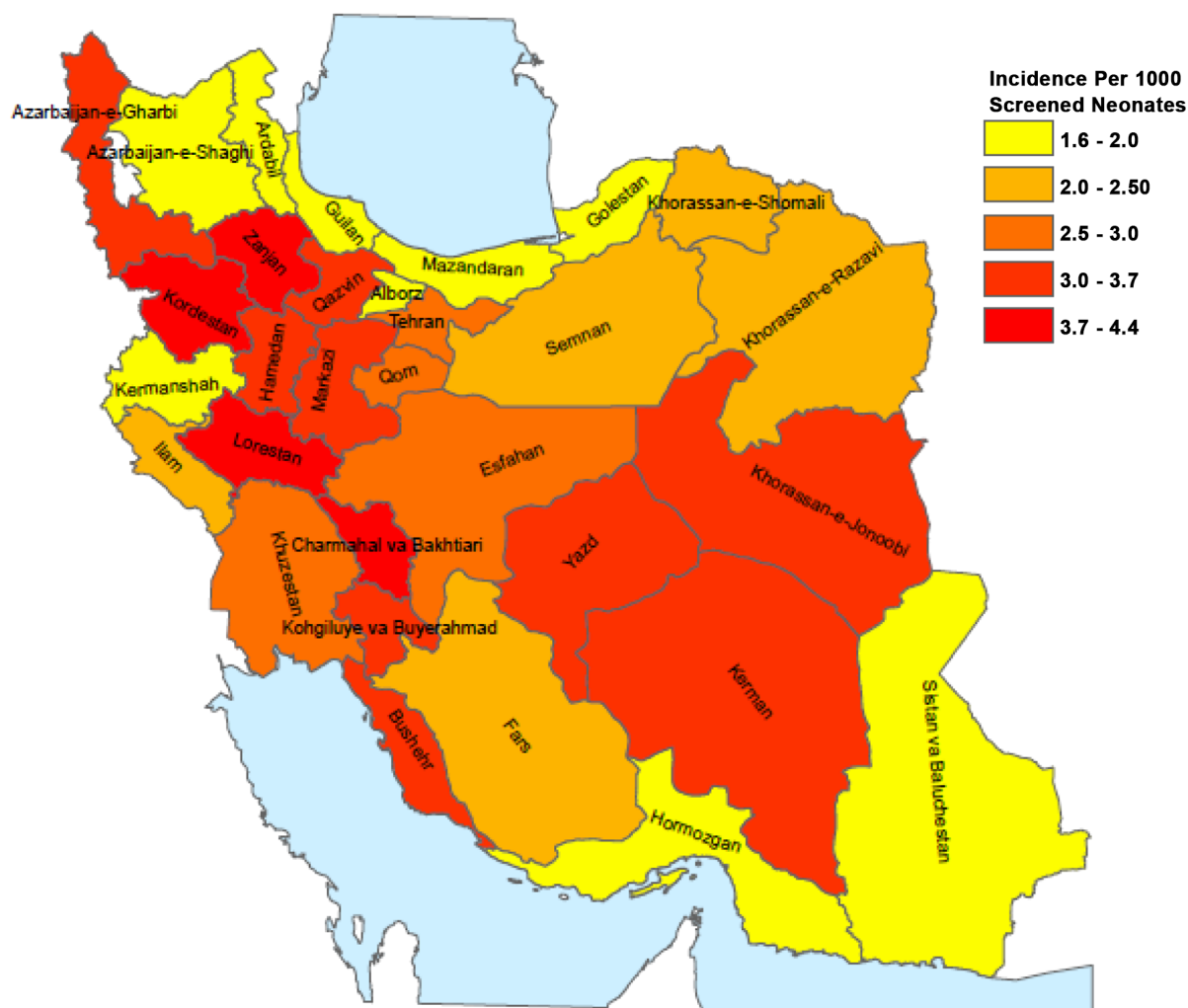


Figure 2. The average incidence rates of congenital hypothyroidism in Iran during 2006 - 2017

5. Conclusions

Newborn screening, as a revolutionary advancement in preventive medicine, offers promising results in preventing the cognitive dysfunction secondary to CH throughout the world. According to existing evidence, detection via newborn screening and treatment of infants with CH have largely eliminated intellectual disabilities such as mental retardation caused by the disorder. Indeed, early diagnosis and timely treatment as the main objectives of CH surveillance are critical to optimizing long-term outcomes. Iran can be considered as one of the successful countries in implementing the neonatal screening program with the aim of prompt detection and treatment of CH cases.

According to the review of documents, structures, and process of the national health system surveillance, we can conclude that the performance of the newborn screening program for CH in Iran is good. However, we need to clarify all components of protocols in details for health care professionals involved in the program. Due to the high incidence rate of CH in Iranian neonates, the continuation of the screening program in the country and also conducting further studies to determine the main risk factors for the high incidence of this congenital error is essential. Our results also suggest that using a TSH threshold of 5 mU/L as the cutoff point during recent years is superior than the primarily national standard (10 mU/L), although due to the high recall rate, the cutoff requires further evaluation to achieve the highest sensitivity with suitable PPV. It should

be noted that an incomplete implementation of the national program with regard to some aspects of premature infants with CH and follow-up of potential false negative cases were the main challenging issue for Iran national newborn screening.

Footnotes

Authors' Contribution: Drafting and finalizing the manuscript: Shahin Yarahmadi, Nasrin Azhang, Bahram Nikkhoo, and Khaled Rahmani.

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