NATIONAL SCREENING FOR CONGENITAL HYPOTHYROIDISM IN PERU: A BROKEN PROGRAM

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ABSTRACT

Congenital hypothyroidism (CH) is the most common cause of preventable intellectual disability. The prevalence of CH varies by geographic region, race, and ethnicity. In the countries of the Northern hemisphere, the prevalence has been reported as 1:4,000 live newborns. The prevalence is remarkably different among countries in Latin America, not only because of their diversity of races and ethnicities, but also because of the notorious heterogeneity in socioeconomic development and health care system in each country. The incidence of CH in 1984 in Peru was reported as 1:1,250. In 2007, the reported incidence by the Instituto Nacional Materno Perinatal (INMP) [National Institute for Maternal and Perinatal Care in Peru] was 1:1,638. A recent retrospective study performed by the Instituto Nacional de Salud del Niño in Lima, Peru described the average age of diagnosis of CH as 5.9±5.28 months. This late age of CH diagnosis certainly is an indicator of the poor efficiency of the current neonatal CH screening programs in Peru. Every Peruvian infant deserves a timely newborn screening and treatment for CH. The Peruvian government is responsible for ensuring this mandatory goal is achieved promptly. (Original article: Huerta-Sáenz L, Del Águila C, Espinoza O, Falen-Boggio J, Mitre N. Tamizaje nacional unificado de hipotiroidismo congénito en el Perú: un programa inexistente. *Rev Peru Med Exp Salud Publica.* 2015;32(3):579-85.)

Key words: Congenital hypothyroidism; neonatal screening; child, Peru (source: MeSH NLM).

FOREWORD

Congenital hypothyroidism (CH) is the most common cause of preventable intellectual disability in the pediatric population. The worldwide prevalence of CH is reported as high as 1:4,000 live births in developed countries of the Northern hemisphere[1]. In Latin America, a study of CH in Argentina from 1997 to 2010 described a prevalence of about 1:2,367-1:3,108 live births[2]. In Peru, the prevalence data for CH are different depending on the specific health care system being surveyed due to a lack of a unified national screening program.

In Peru, there are few published studies on the matter. A recent article on this subject reported CH patients had a late age at diagnosis (5.3±5.9 months), suggesting the poor effectiveness of current neonatal CH screening programs in Peru[3].

The aim of this article is to review the development of the neonatal screening program for congenital hypothyroidism in Peru; to compare how successfully Peru enforces this program in relation to other American countries; to raise awareness among the general population and health professionals about the importance of an effective national CH neonatal screening program; and because of its impact on the population, to suggest possible strategies to improve the age of diagnosis of CH in Peru.

HISTORY OF NEONATAL SCREENING OF CONGENITAL HYPOTHYROIDISM IN PERU

The first legal initiative to launch a national CH screening program in Peru emerged in 1997 through the Ministry of Health (MINSA) Resolution 494-97-SA/DM, in which it was declared that the CH neonatal screening was necessary in all nursery units nationwide [4]. Earlier in the same year, the National Institute of Child Health (*Instituto Nacional de Salud del Niño*, INSN) opened the first CH neonatal screening laboratory in Peru, with state-of-the-art laboratory equipment donated by the JICA (Japan International

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Cooperation Agency) as part of a training program for healthcare professionals in developing countries[5]. This annual 3-month-long course was conducted by the Institute of Public Health of the city of Sapporo, Japan in 1991 thanks to the JICA's International Cooperation Program[6] Unfortunately, this pilot project did not receive any financial support from the Peruvian government and could only be implemented with donations from parents in a mother-baby hospital in Lima[5].

The Edgardo Rebagliati Martins Hospital in Lima was the first healthcare center in Peru to start routine CH neonatal screening in 2002, right after EsSalud (the Peruvian healthcare/social security system) started implementing this strategy at the national level. According to a report published in 2013 by Galan-Rodas, EsSalud's routine neonatal screening program managed to screen 100% of newborns for CH, congenital adrenal hyperplasia (CAH), galactosemia, and phenylketonuria, having screened 476,287 newborns through June 2002[7].

In October 2003, the National Institute for Maternal and Perinatal Care (*Instituto Nacional Materno-Perinatal*, INMP), a national reference hospital for obstetric care in Lima, Peru, started its own neonatal screening program by running a pilot program from October 2003 to February 2004 for the detection of CH, CAH, galactosemia, and phenylketonuria. According to a report published by the INMP in its own institutional website, the program coverage for children born at this center was 98.8% from March 2004 to April 2014[8]. The same article reported that the Ministry of Health lacked the resources needed to implement a similar strategy at the national level and suggested to create 4-5 national reference centers as national leaders for this unified screening program.

The second national initiative was the publication of the National Standards for Comprehensive Child Healthcare NTS 040/MINSA/DGSP-V.01, to be enacted as a Ministerial Resolution on March 20th, 2006. For the first time, this rule described the CH screening as "mandatory" in Peru, describing that "TSH screening should be performed in 100% of newborns at discharge or within the first 60 hours of life through a blood sample taken with the heel-prick method and the subsequent collection on filter paper."[9]

DIAGNOSIS OF CONGENITAL HYPOTHYROIDISM

The diagnosis of CH is performed through thyroid function tests (TFTs), specifically by measuring plasma thyroid stimulating hormone (TSH) and/or free thyroxine (T4). Both tests should be collected after the first 48 hours of life to avoid falsely elevated TSH or free T4 values due to their expected physiological increase after birth[10].

Before obtaining plasma samples for CH confirmation tests, a CH neonatal screening test should be performed on filter paper with blood obtained with the heel-prick method. The sample collected on filter paper must be collected after the first 24 hours of life under ideal conditions [11]. In some countries, cord blood samples are also used for CH screening tests. TFT results obtained from filter paper samples can report TSH, free T4, or total T4, depending on the requirements of each program. Normal reference ranges should be defined according to the specific populations.

Some countries such as Canada, Japan, Australia, and some European countries use TSH as the only CH screening test [10], but in other countries, such as Puerto Rico and in some states of the USA, both TSH and free T4 are used [10]. An elevated TSH and/or a low-to-normal free T4 screening test results are suggestive of CH, and the diagnosis should be confirmed with plasma TSH and free T4 tests. If the confirmation tests are abnormal, then thyroid hormone replacement therapy should be started immediately. In the US, all newborns undergo CH neonatal screening before hospital discharge. Some states also perform a double screening: 1) A first screening between the first 2-4 days of age, and 2) a second screening at 2 weeks of age to detect possible cases of mild or late increases in TSH values [12].

"Normal" reference values should be obtained with standardization techniques from laboratories specialized in hormone tests, and should take into consideration the patient's specific age because the TSH level is usually elevated in the first weeks and even months of life. Standardized normal value ranges for TSH, free T4, and total T3 and T4 have been previously published and validated [10].

In February 2014, the European Society of Pediatric Endocrinology (ESPE) issued new consensus guidelines for screening, diagnosis, and treatment of CH. According to these guidelines, if the TSH neonatal screening test result is equal to or greater than 40 mU/L, it is recommended to start treatment as soon as a blood sample for a confirmatory test is collected, unless serum TFT results are available the same day the neonatal screening test results are notified[13].

IMPORTANCE OF TIMELY DIAGNOSIS OF CONGENITAL HYPOTHYROIDISM

The primary rationale for the need of immediate treatment in confirmed cases of CH is the fact that in early childhood (first 3 years of life), brain development is

critically dependent on thyroid hormone[1]. Delays in the treatment of CH can cause deterioration of the brain function, intellectual quotient (IQ) impairment, and/or alteration of normal psychomotor development[14].

The symptoms of CH are nonspecific, especially in the earliest stages of life; therefore, the most successful strategy to identify CH before hypothyroxinemia causes irreversible brain sequelae is obtaining TFTs in every newborn as soon as possible after birth.

In 1986, the medical bulletin of the Mexican Children's Hospital published a clinical scale created by Blanco-Lopez for the assessment of patients with suspected CH on the basis on a previously published study by Letarte[15]. This clinical scale described signs and symptoms such as: dry skin, hypotonia, large anterior fontanelle, constipation, prolonged jaundice, etc., as suggestive of CH. The maximum score was 21 and the report recommended to suspect CH if the patient's score was equal to or greater than 4. During the decade of 1980, when most Latin American countries did not have laboratories with up-to-date technology for the neonatal screening of CH or even TFTs, this clinical scale helped identify patients with symptoms or signs compatible with CH. Currently, this type of clinical scale is unreliable for the early diagnosis of CH, because infants with CH often have abnormal TSH levels long before clinical symptoms or signs are evident.

Around 1961-1963, countries like Canada, England, USA, and Japan understood the importance of promoting national policies of neonatal screening for the early identification of certain congenital diseases in newborns which, without a prompt initiation of treatment, could potentially develop serious sequelae such as developmental delay (intellectual disability), severe neurological damage, metabolic derangements, and permanent disability. The first neonatal CH screening program was created in Canada in 1974 and later instituted in the US in 1975 in the wake of a successful pilot program conducted in Pittsburgh, Pennsylvania, USA[16]. After the neonatal CH screening program was started in the USA, the detection of newborns with CH in this country progressively increased from 1:4,094 in 1987 to 1:2,372 in 2002[17].

NEONATAL CONGENITAL HYPOTHYROIDISM SCREENING PROGRAMS

NEONATAL CONGENITAL HYPOTHYROIDISM SCREENING IN THE USA

In 2006, the American Academy of Pediatrics (AAP) published updated guidelines for the neonatal screening and treatment of CH(18). The AAP statement not only described the reasons why a neonatal screening program for CH needed to be "efficient" in order to be successful, but also proposed specific clinical guidelines for therapeutic decision-making, based on TSH and free T4 levels. It also issued controversies regarding the treatment of cases with borderline TSH levels between 6-10 mU/L. An important section of the AAP statement described how to report TFT results and how to follow up abnormal screening tests. According to these guidelines, CH screening test results should be notified by the laboratory to the hospital unit or physician who ordered them. By establishing guidelines for an appropriate monitoring process, the statement ensured that patients with abnormal screening test results could be notified promptly and recommended to start early treatment. Additionally, the guidelines determined that the physician who indicated the screening tests was "responsible to notify" the patient's parents about the results; and in cases when the physician could not be located, the final responsibility resided with the healthcare facility where this physician worked. This strategy was devised to ensure the appropriate monitoring and prompt treatment of CH.

NEONATAL CONGENITAL HYPOTHYROIDISM SCREENING IN EUROPE

As previously described, the European Society for Pediatric Endocrinology (ESPE) recently issued consensus clinical guidelines for the screening, diagnosis, and treatment of CH. These guidelines, unlike the AAP guidelines, emphasize not only the importance of a "mandatory" neonatal CH screening, but also the importance of genetic counseling if there is a family history of thyroid disease or associated congenital birth defects, the importance of prescribing thyroid hormone replacement therapy in cases of transient hypothyroidism, and the importance of continuous evaluation of neurological and neurosensory development, specifically hearing impairment and language delays. These two conditions are more frequent in infants with CH[13].

NEONATAL CONGENITAL HYPOTHYROIDISM SCREENING IN LATIN AMERICA

In Latin America, current neonatal screening programs, including CH screening, are diverse and remarkably heterogeneous. In 2007, Borrajo published an article about the status of the neonatal screening programs in Latin America in the early 21st century and described in detail the diverse cultural, ethnic, and demographic heterogeneity in most of Latin American countries and the different healthcare systems in charge of the neonatal screening programs[19]. These different features in form and implementation of national screening programs led him to classify Latin American countries in 6 different groups:

- Group I: Cuba, Costa Rica, Chile, and Uruguay: Higher level of development, national coverage rates of about 100%, the government is directly responsible for the screening, treatment, and monitoring.
- Group II: Brazil, Mexico, and Argentina: National coverage rates of 60-80%; the private sector is the main responsible for implementing and financing the program.
- Group III: Colombia, Paraguay, and Venezuela: Screening programs were first implemented in 1999.
- Group IV: Nicaragua and Peru: National policies were first implemented in 2005, and the national coverage rates of only 4-6%.
- Group V: Guatemala, Dominican Republic, Bolivia, Panama, and Ecuador: They had no national neonatal screening programs and screening tests were financed only in the private sector healthcare facilities with coverage rates below 1%.
- Group VI: El Salvador, Honduras, and Haiti: Neonatal screening programs were almost nonexistent.

These groups, from highest to lowest value, are correlated with the degree of economic development in these countries. In the same article, it was reported that Peru had a low national neonatal screening coverage of only 3.9%, and that the financial support for the program came partially from the central government and the healthcare/social security system (EsSalud), with specific legal standards for the CH neonatal screening program in 2005. This low coverage rate in Peru was abysmally lower than the national coverage rate reported by Argentina in the same year (64%).

NEONATAL CONGENITAL HYPOTHYROIDISM SCREENING IN PERU

In Peru, the mandatory legal standard for neonatal screening of CH has existed since 2006, as described above. However, there is no national CH screening program that can integrate all existing healthcare subsystems to run the CH screening as a whole. Therefore, there is no single surveillance organization that is responsible for monitoring goal achievement and measuring the program's success rates (9), because every subsystem executes their own CH screening programs independently. There are four different healthcare subsystems in Peru: 1) EsSalud (social security-funded); 2) the Ministry of Health (MINSA, government-funded); 3) the armed forces and police healthcare administrations, and 4) private healthcare organizations. The four of them should be monitored by a single public agency to make sure that the program fulfills a 100% coverage nationwide and not just within a specific subsystem. The integration of the neonatal CH screening programs across all four healthcare subsystems is certainly a major challenge, but it is mandatory to overcome this challenge in order to create a unified national screening program and achieve the desired national coverage goals.

Other requirements to ensure the national program's success include the use of appropriate laboratory techniques, the standardization of normal TSH and free T4 values across laboratories, and a verification system to ensure both the prompt notification of test results to the patients' parents and the confirmation of immediate treatment initiation after confirmatory test results have been reported as positive.

Ideally, all infants with confirmed CH should have follow-up visits with a specialist, that is, a pediatric endocrinologist. Given the fact that Peru does not have enough pediatric endocrinologists, one alternative would be to continue including Pediatric Endocrinology as a mandatory rotation in the Pediatrics residency curriculum, or to include this rotation as part of the Family Medicine residency curriculum and the annual training for the physicians starting the SERUMS (a year of mandatory service in underserved, rural areas right after graduation from medical school). All these steps require strategic planning and the integrated participation of the aforementioned four health subsystems. It is important that the national CH screening program remains in effect independently of the government and/or the ruling political party.

UNIFIED NATIONAL CONGENITAL HYPOTHYROIDISM SCREENING IN PERU: A NATIONAL PRIORITY

A national unified CH screening program should be an integrated, nationwide program in which each existing health subsystem in Peru would have an obligation to periodically report data about CH screening and diagnostic test results to a specific public agency for the purpose of national surveillance and monitoring (the authors suggest this office be created as a part of the Ministry of Health). This specific public agency would represent the Peruvian government and would be responsible for training laboratory personnel in charge of processing the filter-paper blood samples in all relevant facilities of the four health subsystems, in order to standardize the laboratory screening procedures (that is, that all laboratories process the samples in a similar manner). We also think it is necessary to implement a laboratory network with regional laboratories monitored by a central laboratory. All laboratory staff should be given specific training and equipment for the screening process from a single national regulatory office.

Similarly, each health subsystem should have a leader responsible for its specific CH screening program and who would integrate a national expert panel; this panel should be the head of the unified national screening program in the country. The unified national screening program may start running a pilot program, whose results could be measured for a subsequent translation into a fully-operating national screening program. If successful, this model could later be considered as an example to implement other neonatal screening programs in Peru.

We recommend considering the following additional steps in the implementation of the unified CH screening program:

a) Use similar laboratory techniques and procedures to process CH screening tests in all approved laboratories in each of the four health care subsystems.

b) Guarantee the mandatory report of test results to the relevant regulatory office.

c) This regulatory office should be responsible for reporting the relevant test results to the patients' families and/or the healthcare facility where the screening tests were performed, and should also be responsible for providing specific treatment recommendations and coordinate a follow-up visit with a pediatric endocrinologist or a trained healthcare professional within 2-4 weeks after initiation of treatment.

The authors believe that the development of a unified national CH screening program is a national priority in Peru. However, opinion should be based on evidence. Therefore, the next question would be, what is the national prevalence of congenital hypothyroidism in Peru?

The first CH prevalence report in Peru was published in 1984 by Rojas, Garmendia *et al*. The prevalence of CH in this report was 1:1,250 [20]. This study was conducted on a sample of 1,254 live births at the Maternity Hospital of Lima (now INMP) and the Dos de Mayo Hospital in July-August 1983. Twenty years after the Ministry of Health issued the first ministerial resolution addressing CH screening in Peru, the INMP reported an incidence of 1:1,638 live births in 2007 [21].

The age of diagnosis and treatment of CH can be used as an indirect measurement of the success of the CH screening program. The first studies on the subject were described by the Department of Pediatric Endocrinology at the National Institute of Child Health (INSN) in a cohort study between 1981 and 1990. According to a study of this cohort by Del Aguila *et al*, the average age of clinical diagnosis of CH was 17 months [22]. These numbers were really striking. A subsequent study done at the same hospital and the same department between 1995 and 2005 worked on an initial sample of 247 medical charts of patients with presumptive CH diagnosis. The final study population included only 37 of these medical records due to specific inclusion criteria; the average age of CH diagnosis in this study was 5.9±5.3 months [3]. These important data were provided by the INSN, the main national reference pediatric center for the MINSA.

Indeed, the average age of diagnosis appears to have improved from 1990 to 2005. The issuing of the first regulatory standard for CH screening in 1997, together with the fact that a greater number of pediatricians had been trained in CH diagnosis in the meantime, would have translated into a reduction in the average diagnosis age for CH. However, it is regrettable that these patients had been referred to the INSN for CH diagnosis in such a delayed manner.

The timely diagnosis and treatment of CH involves starting treatment immediately after diagnosis, but ideally within the first 2 weeks of life, with the aim of bringing free T4 levels closer to normal as soon as possible [13]. Consequently, despite having improved the age of clinical diagnosis of CH in the last 20 years, Peru is still far from the goal of preventing irreversible sequelae due to a late CH diagnosis. An early diagnosis, an immediate treatment initiation, and a rapid normalization of the TFT values are required to achieve optimal neurological outcomes in all CH patients.

A study by Selva, La Franchi, et al. compared the neurological development of patients with CH, specifically evaluating the cognitive level, academic performance, attention, and behavior in 3 groups of patients. Each group received different doses of thyroid hormone replacement and TFTs were found to reach normal values within different times after treatment initiation. Those patients whose TFT normalization took longer presented with speech delay problems more frequently than those whose TFTs reached normal values in a shorter period [23].

In Peru, the National Institute of Statistics and Information Technology (Instituto Nacional de Estadística e Informática, INEI) reported a total of 794,040 births in 2011[24]. If the CH incidence previously reported by the INMP (1:1,638) is extrapolated, it can be calculated that 485 infants with CH would be born each year, and without a timely diagnosis and treatment, the same 485 infants would later be diagnosed with developmental delay or neurocognitive/sensorineural deficits. Our deficiencies in the management of this problem at the national level will continue to allow the birth of multiple generations of Peruvian children with developmental delay and disability, unless we start solving this problem soon.

It will take several years of concerted efforts to achieve a 100% national coverage rate for early CH screening and treatment, but this goal is attainable if this problem is addressed as a national priority. This goal will be achieved not only by educating health care professionals -that is, medical students, SERUMS physicians (primary care providers from underserved areas), general practitioners, residents, pediatricians, Ob/Gyn physicians, nurses, midwives, etc.- on this topic, but also by informing the general population about this problem and their right to an appropriate health care.

CONCLUSIONS

Every Peruvian child from all social strata deserves to have access to a national CH neonatal screening program and the opportunity of an early CH diagnosis and initiation of treatment to avoid preventable intellectual disabilities. The establishment of a unified national CH screening, diagnosis,

and treatment program is certainly a challenging goal, but without a doubt it is necessary if we want to make progress as a country.

Every Peruvian child, regardless of place of origin, health insurance, socioeconomic level, or ethnicity deserves the chance to grow to their full neurocognitive potential. The Peruvian government, as the national entity responsible for the health of the Peruvian population, is primarily responsible for reaching this goal. Thus, the Ministry of Health is the institution responsible for ensuring that this goal is met.

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