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Screening for congenital hypothyroidism: A worldwide view of strategies

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Detection by newborn screening (NBS) and treatment of babies with congenital hypothyroidism (CH) has largely eliminated the intellectual disability caused by this disorder. Lowering of the screening TSH cutoff and changes in birth demographics have been associated with an approximate doubling of the incidence of CH, from 1:3500 to 1:1714. The additional cases detected by lowering of the TSH cutoff tend to have milder hypothyroidism, with imaging often demonstrating a eutopic, "gland in-situ", and some cases turn out to have transient CH. Based on our search for current screening programs, approximately 71 percent of babies worldwide are not born in an area with an established NBS program, despite the existence of screening for over five decades in developed countries. Thus, the majority of babies with CH worldwide are not detected and treated early, such that the economic burden of retardation owing to CH remains a significant public health challenge.

Introduction

Congenital hypothyroidism (CH), with a reported incidence in 1:2000 to 1:4000 newborns, is one of the most common preventable causes of mental retardation.[1] Most neonates with CH do not have obvious manifestations of hypothyroidism at birth, both because many have some residual thyroid function and partial transplacental passage of maternal thyroid hormone offers temporary protection.[2] Clinical

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diagnosis therefore usually is delayed until 3 months of age or older, by which time some effects of thyroid hormone deficiency on the developing brain may be irreversible. Thyroid function tests added to newborn screening (NBS) programs beginning in the mid-1970s facilitated early detection and treatment of neonates with CH,[3] largely eliminating the neurodevelopmental impairment from hypothyroidism.

The chief objective of NBS programs is to detect neonates with primary CH. Both a primary T4-reflex TSH test strategy or a primary TSH test strategy detect infants with primary CH. Only the primary T4 test approach has the potential to detect neonates with secondary (central) CH.[4]

As NBS programs gained experience with detection of neonates with CH, some elected to lower the screening TSH cutoff. Lowering of the TSH cutoff led to a higher incidence of CH, primarily explained by the detection of milder cases, many characterized by a eutopic, normally formed thyroid "gland-in-situ".[5] Detection of milder forms of CH has refocused attention on the initial intent of NBS, prevention of mental retardation. Lowering of the TSH cutoff increased the labor and economic burden of NBS programs, but it is not clear that these milder (often transient) cases of CH benefit from early detection and treatment.[6]

This article will present the history of screening test strategies for CH, discuss the current status of screening around the world, review changes in the epidemiology of CH over the four decades of screening, discuss the impact that lowering of TSH cutoffs has had on the incidence of CH and changes in percentage of different etiologies, briefly summarize treatment and outcome, and finally examine the "cost-effectiveness" of current screening strategies to detect neonates with CH. It should be emphasized that, despite almost 50 years since the introduction of NBS, the majority of babies worldwide are not born in a location with an established NBS program. Thus, the majority of babies with CH worldwide are not detected and treated early, such that the economic burden of retardation owing to CH remains a significant public health challenge.

History of screening test strategies for congenital hypothyroidism

With the addition of tests to detect CH in the 1970s and 1980s, most NBS programs performed a T4 test, followed by a TSH determination on infants with a T4 below a specified cutoff (typically <10th percentile, though currently the Netherlands <20th percentile), while some programs performed an initial TSH test.[7] With increasing accuracy of TSH measurements on the small volume of blood available in the dried blood specimens obtained for screening, several programs employing a primary T4 test switched to a primary TSH test.[4] A minority of programs have elected to undertake simultaneous T4 and TSH testing. Finally, some programs in Japan report measuring free T4 in the dried blood spot specimen[8]; as might be predicted, this strategy likely has the best potential to detect central CH.

As less developed countries gained the resources to undertake newborn screening in the 1990s and later, nearly all used a primary TSH test. Currently, most NBS around the world employ a primary TSH strategy, the exceptions being some state programs in the United States (U.S.), Israel, the Netherlands and some programs in Japan (the latter, as noted above, measuring free T4 in the dried blood spot).

Current status of screening programs for congenital hypothyroidism around the world

Primary congenital hypothyroidism

In order to estimate the percentage of the world birth population that is currently being screened for CH, we undertook a search for all existing newborn screening programs worldwide in countries with a population greater than one million. Data was gathered using PubMed searches using key terms and where applicable additional sources were found via Google searches using the same terms. Search terms used in conjunction with the name of the respective country and included "hypothyroidism, congenital hypothyroidism, newborn screen, and neonatal screen." Based on identified articles used with these search methods data was organized by region in Tables 1A–D. Population figures in the tables are based on the most recent estimate or projections by the national census authority (http://www.census.gov/aboutus/stat_int.html) where available and usually rounded off. Where there is not updated national data available, figures are based on the 2012 estimates by the Population Division of the United Nations Department of Economic and Social Affairs (http://www.un.org/esa/population/). Annual Births were estimated using the United Nations, Department of Economic and Social Affairs,