Future Research Directions to Identify Causes of the Increasing Incidence Rate of Congenital Hypothyroidism in the United States

abstract

A workshop to evaluate the reported increasing trend in the incidence rate of primary congenital hypothyroidism (CH) identified by newborn screening was held February 27 and 28, 2008, in Atlanta, Georgia, and was sponsored by the Centers for Disease Control and Prevention, the Health Resources and Services Administration, and the National Newborn Screening and Genetics Resource Center. Through a series of presentations and discussions, this group of experts considered a variety of factors that could be contributing to the perceived increasing trend of the CH-incidence rate, the gaps in knowledge that need to be overcome to identify the causes of the observed trend, and possible future research activities that might resolve the uncertainties surrounding the increasing incidence rate of CH in the United States. On the basis of these discussions, workshop participants concluded that the initial focus of future efforts should be to determine if the increasing CH-incidence rate persists once there is standardization of the diagnostic criteria for the classification of CH versus transient hypothyroidism. In discussions, workshop participants suggested that if the increasing incidence rate of CH could not be explained by definitional issues, then future research could focus on the identification and evaluation of risk factors for CH that might be changing among the US population and, thus, contributing to the observed increasing incidence rate of CH. *Pediatrics* 2010;125:S64–S68

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KEY WORDS

hypothyroidism, incidence, newborn screening, diagnosis, risk factor, public health

ABBREVIATIONS

CH—primary congenital hypothyroidism
NBS—newborn screening
T4—thyroxine
TSH—thyrotropin

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In 2008, a 2-day workshop of experts was held in Atlanta, Georgia, to evaluate the reported increasing incidence rate of newborns with primary congenital hypothyroidism (CH) identified by newborn screening (NBS) in the United States (for a summary of the workshop presentations, see the article by Olney et al[1]). The workshop culminated with a discussion among participants of the gaps in knowledge toward understanding the causes of the reported increasing incidence rate of newborns with CH, as well as potential future directions in research that might resolve the questions surrounding the upward trend. Participants concluded that the principal question to be addressed is whether the incidence rate of newborns with CH truly is increasing in the United States, as reported by Harris and Pass,[2] or whether methodologic issues in the diagnosis and management of CH are contributing to a perceived increasing trend. The participants also believed that there is a need to determine if other risk factors might be associated with the increase if the increasing incidence rate cannot be explained by methodologic factors. Finally, participants questioned whether there are modifiable risk factors for CH that can be addressed through public health interventions.

PRECISE DEFINITIONS FOR CH AND TRANSIENT HYPOTHYROIDISM

To determine if the incidence rate of newborns with CH is truly increasing, participants stressed that a precise definition for CH is required and that cases of CH must be identified on the basis of consistent diagnostic criteria. One concern was that inconsistencies in diagnosis and lack of long-term follow-up of cases of CH by NBS programs have led to the erroneous inclusion of cases of transient hypothyroidism in the total counts of CH. Evaluating the possibility of erroneous inclusion of cases of transient hypothyroidism in the total counts of CH has been complicated by the fact that the definition of transient hypothyroidism varies appreciably among state NBS laboratories.[3] In addition, follow-up staff might not necessarily be informed by the endocrinologist or primary care provider that a case of CH was subsequently determined to be transient, which is reflected in the fact that the reported incidence rate of transient hypothyroidism varies widely between state NBS programs.[4] Therefore, perhaps newborns with transient hypothyroidism are being misclassified as having true CH, and if this misclassification has become more common over time, it conceivably could be contributing to the observed increasing trend of CH-incidence rate. In addition, if misclassification of cases of hypothyroidism is at issue, the increasing trend would be an indication of the need for improved communication practices around the follow-up component of the NBS system. Therefore, workshop participants recognized the need for preferably prospective, long-term follow-up of cases of CH to standardize the clinical and laboratory criteria that are used to reclassify children as having had transient hypothyroidism, to record a final diagnostic disposition, and to obtain accurate counts of true CH. For a discussion of the effects of transient hypothyroidism on the incidence rate of newborns with CH, see the article by Parks et al.[5]

Since the workshop, a project has been undertaken that focuses on long-term follow-up of CH to discriminate transient hypothyroidism from true cases of CH and to link outcomes to initial diagnosis. The National Newborn Screening and Genetics Resource Center, funded by the Health Resources and Services Administration, Maternal and Child Health Bureau, Genetic Services Branch, recently funded the New England Newborn Screening Program (Massachusetts) to follow-up 2 cohorts of children diagnosed with CH (birth years 1987–1991 and 2001–2003) to determine the final diagnostic disposition of each child (ie, transient hypothyroidism versus true CH) and to document other maternal and newborn factors that potentially affect thyroid function.

CONSENSUS SERUM THYROID-FUNCTION TEST CRITERIA FOR DIAGNOSIS OF PRIMARY, SECONDARY, AND TRANSIENT HYPOTHYROIDISM

The issue of misclassification of transient hypothyroidism aside, the workshop participants focused on the standardization of the diagnostic criteria for CH. Although a 2006 report of the American Academy of Pediatrics provided specific recommendations to guide the confirmatory process for newborns with a positive newborn screen for CH,[6] there is significant variability among practitioners regarding the confirmatory tests that are performed and the decision process for determining if a newborn has CH on the basis of particular serum concentrations of total thyroxine (T4), free T4, and thyrotropin (TSH). Most of the data on clinical practice are unpublished. However, a study from Wisconsin that surveyed physicians of record for 500 newborns with abnormal NBS test results for hypothyroidism in 1984–1985 revealed that for confirmatory testing only 87% of newborns had a serum T4 assay performed, 82% had a TSH assay, 9.5% had a free T4 assay, 5.1% had thyroid imaging, and 4.4% had no follow-up studies.[7]

Another concern raised by workshop participants was that when practitioners obtain these analytes to determine the diagnosis or to "clear" the newborn of the abnormal NBS test result, the concentrations of the analytes

are not necessarily reported to NBS follow-up programs. Even if feedback is received by the NBS follow-up program, the medical provider might only inform the program that the newborn was "cleared" or that the infant was confirmed to have primary or secondary congenital hypothyroidism and was started on treatment; the criteria on which the diagnosis was based might not be communicated.

Workshop participants suggested that a protocol for collecting common data elements could be developed for use by NBS programs to elicit and record the diagnostic analyte concentrations, and that those concentrations could be correlated with the clinical outcome. Such a protocol could be run as a pilot project by several NBS programs to document regional practices used by primary care providers, as well as endocrinologists, for confirming a diagnosis of CH. This process could provide insights into the criteria that actually are being used in the community to diagnose and treat CH. These data also might show whether CH is being "overdiagnosed" and, thus, contributing to the observed increasing incidence rate. The results from such pilot studies could serve as a resource for the appropriate North American professional societies to recommend the use of specific common case definitions of primary, secondary, and transient hypothyroidism, as well as the laboratory criteria for confirming the diagnosis of each of these conditions.

DIAGNOSTIC IMAGING TO IDENTIFY THE ETIOLOGY AND INCIDENCE RATE OF CH

CH is not a single disorder, because the end effect can be a result of multiple etiologies, such as ectopic thyroid gland, absent gland, dyshormonogenesis, or resistance to TSH. It is not known whether in the United States the incidence rate of 1 or more of these disorders is increasing, because thyroid imaging by either ultrasound or radionuclide studies is considered optional[6] and performed infrequently. However, when performed routinely for newborns with CH, variations in the proportion of thyroid gland dysplasia (absence or ectopia) have been observed. In a study in California, Schoen et al reported that 57% of 210 newborns with CH had dysplastic thyroid glands by scintigraphy,[8] which was lower than the expected frequency of 80% to 85%[9] (although between different studies there was reported variation according to race and ethnicity, sex, and the scintigraphy technique[8,10,11]). As expected, newborns who were subsequently classified as having transient hypothyroidism had a normal-appearing thyroid gland by neonatal scintigraphy, although the majority of newborns with normal-appearing thyroid glands by scintigraphy had true CH.[8] If the increasing incidence rate of CH is attributable partly to misclassification of transient hypothyroidism as true CH, then one would expect that the proportion of normal-appearing thyroid glands among cases of CH would be higher than expected. To evaluate this hypothesis, and to collect data on the frequencies of the various thyroid disorders and provide potential insight into the increasing CH-incidence rate, a protocol could be developed to evaluate thyroid gland dysgenesis versus normal-appearing glands among newborns identified with CH by NBS programs in several states. These neonatal evaluations would then be linked to long-term follow-up so that the final disposition (transient hypothyroidism versus true CH) could be correlated with initial neonatal analyte concentrations and scan results. Several years of such evaluations among newborns with CH of diverse races and ethnicities could address the misclassification issue and also might indicate areas for further study if the incidence rate of thyroid dysgenesis is found to be increasing among certain racial or ethnic groups.

POTENTIAL EFFECTS OF EPIDEMIOLOGIC RISK FACTORS ON THE INCIDENCE RATE OF CH

In addition to considering the overdiagnosis and misclassification of CH as potential methodologic factors that contribute to the increasing CH-incidence rate, workshop participants also discussed etiologic risk factors for CH that need further evaluation, as well as possible approaches for investigating such risk factors. Several risk factors have been associated with the increased occurrence of CH, including female sex; Hispanic, Asian, and Native Hawaiian or other Pacific Islander race or ethnicity; low birth weight; preterm birth; high birth weight; advanced gestational age; twin gestation; and family history of goiter or hypothyroidism.[12–14] Although none of these risk factors have been associated directly with the observed increasing incidence rate of CH in the United States,[2] the contribution of each of these factors (particularly race and ethnicity and preterm births or low birth weight) needs to be explored more fully (as indicated in the article by Hinton et al[15]). In addition, preterm birth, low birth weight, and multiple-parity pregnancies are interrelated, as are high birth weight and advanced gestational age, so future studies should collect data on all of these potential risk factors, and analyses should be performed that take into account these covariates.

POTENTIAL EFFECTS OF REDUCED MATERNAL IODINE INTAKE ON CH-INCIDENCE RATE

Unknown or understudied environmental risk factors should be sought and evaluated, particularly modifiable

risk factors that are amenable to public health interventions. For example, the workshop participants discussed maternal iodine deficiency as a potential risk factor for CH in the newborn.[16] They also observed that median urinary iodine concentrations among women of reproductive age in the United States declined from 1971 to 1994, although the median concentration apparently has stabilized since 2000 according to the National Health and Nutrition Examination Survey (NHANES).[17,18] One approach to evaluating this risk factor might be to partner with NBS laboratories that measure TSH as the principal screening analyte and compare the distributions of TSH values among the newborn population over time with the TSH values among pregnant women who participate in a population-based study (such as the NHANES). The rationale for such a study is that (1) TSH can be a sensitive indicator of iodine deficiency at the population level, and (2) a changing distribution of newborn TSH concentrations might correlate with the trend over time in the proportion of women with iodine deficiency, which suggests a potential relationship between maternal iodine concentrations and newborn hypothyroidism that would merit further investigation.

Another potential study proposed by the workshop participants would be an investigation of maternal hypothyroidism (from iodine deficiency or other causes) as a risk factor for CH by using a unique resource in California. There, maternal midpregnancy serum samples are collected and stored for ~100 000 women each year; once newborns are identified as having CH, it would be possible to go back to the corresponding maternal serum samples and test them for the markers of hypothyroidism.

UNKNOWN RISK FACTORS AND CH-INCIDENCE RATE

The workshop participants realized that there might be risk factors not yet identified or adequately investigated thus far that could be analyzed through population-based epidemiologic studies. Such ongoing studies that potentially could integrate CH as an outcome include the National Birth Defects Prevention Study, a multicenter case-control study of environmental and genetic risk factors for birth defects of unknown etiology,[19] and the National Children's Study, a multicenter, nationally representative cohort study of environmental and genetic risk factors among pregnant women and their children on childhood health and developmental outcomes from the prenatal period through the postnatal age of 21 years.[20,21] The workshop participants concluded that there are likely to be multiple causes of CH, both genetic and environmental, and that studies of gene-environment interactions might require future consideration.

CONCLUSIONS

The immediate concern, the observed increasing incidence rate of CH, will require investigations to clarify existing practices for confirming a diagnosis of CH among all screen-positive newborns, as well as epidemiologic and laboratory-based studies of known and suspected risk factors that might be contributing to the trend. Because it is likely that no single factor underlies the observed increasing incidence rate of CH, as elaborated on in the articles of Hinton et al[15] and Hertzberg et al,[22] the workshop participants have recommended a multipronged investigative approach: long-term follow-up of cases of CH to obtain accurate counts of true CH versus transient hypothyroidism; epidemiologic studies of known risk factors for CH (eg, race and ethnicity, preterm births, and maternal hypothyroidism) that have changing frequencies among the US population and might account for changes in the CH-incidence rate; and epidemiologic population-based evaluations of risk factors for CH that have not yet been identified. Only by closing these gaps in knowledge can appropriate public health interventions be undertaken to address any true changes in the incidence rate of CH.

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