Congenital Hypothyroidism: Inside Ireland's Incline

Stephen H. LaFranchi, MD

The incidence of congenital hypothyroidism diagnosed after clinical presentation is 1:7000 to 1:10 000.[1] As detected by newborn screening (NBS) programs starting in the mid-1970s, the incidence increased to 1:3800 to 1:4000,[2] presumably reflecting detection of all cases. Then, between 2002 and 2010, several NBS programs in the United States[3] and around the world[4–6] reported a doubling of the incidence to 1:2000. What explains this rather dramatic increase over a few decades? In a workshop sponsored by the US Centers for Disease Control and Prevention and the National Newborn Screening and Genetics Resource Center held in 2008, several factors were found:

- Lowering the cutoff for screening thyroid-stimulating hormone (TSH): In Lombardy, Italy, lowering the screening TSH cutoff from 20 to 12 mU/L (1999) and then to 10 mU/L (2002) (whole blood), increased the incidence of congenital hypothyroidism from 1:2654 to 1:1816 and then to 1:1154[5];
- Changes in screening population demographics: The incidence of congenital hypothyroidism is reported to be higher in Asian American, South Pacific, American Indian, and Hispanic infants as compared with white infants[7]; and
- Increase in the percentage of preterm births: In the report from the United States (1987–2000), there was a 23% increase in infants <1500 g, associated with a higher incidence with lower birth weight (>2500 g = 1:1843, 1500–2500 g = 1:851, <1500 g = 1:396).[3]

In this issue of *Pediatrics*, McGrath et al[8] report a unique study, capturing all infants with congenital hypothyroidism from a single country, the Republic of Ireland, detected by a single center from the inception of screening, from 1979 to 2016. Dividing this time period into thirds, McGrath et al[8] report that the incidence increased from 0.27 out of 1000 live births (1:3703) to 0.41 out of 1000 (1:2439) to 0.65 out of 1000 (1:1538). The authors state that their screening protocol, TSH measurement on specimens collected at 72 to 120 hours of age, with a cutoff of >15 mU/L (whole blood), was unchanged over this entire time period. In addition, the investigators report that the increased incidence was associated with detection of a greater proportion of cases with mild hypothyroidism, as judged by lower serum TSH and higher free thyroxine levels, a normal (or hyperplastic) thyroid gland, and transient hypothyroidism. Imaging showed that 23% of cases in period 2 fell in the normal and/or hyperplasia category, increasing to 47% in period 3.

What might explain the more than doubling of the incidence over the 37-year study period? In contrast to explanations noted above, the investigators report that there were no changes in the TSH cutoff, instrumentation, or assay calibration. In addition, they state that screening was undertaken in a relatively homogeneous white population, with no significant change in the racial and/or ethnic makeup of newborns. The investigators do note an increase in preterm infants, which accounted for

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3.9% of cases in period 2 and 15.4% of cases in period 3.

A potential cause of mild, transient congenital hypothyroidism with a normal thyroid gland on imaging is maternal iodine deficiency. Ireland does not have a national salt iodization program. In studies of population iodine status, researchers showed median urinary iodine of 105 μg/L in 1989 and 62.9 μg/L in 2005.[9] In addition, one-quarter to one-half of pregnant women met criteria for iodine deficiency, depending on the season studied.

What else might explain the increasing detection of milder cases? Most NBS programs in the United States use age-related TSH cutoffs, necessitated by the surge in serum TSH peaking at 60 mU/L after delivery, combined with specimen collection at 24 to 48 hours of age, before discharge from the hospital. Age-related TSH cutoffs are necessary to reduce the number of false-positive test results. Although TSH measurement was performed on specimens collected at 72 to 120 hours of age, if there was a shift to earlier collection, even within the 72 to 120 hours of life over the 3 study periods, it is possible that using the same TSH cutoff of 15 mU/L might have led to increased detection of milder, transient cases.

Likely, there are several factors contributing to the more than doubling of the incidence of congenital hypothyroidism over the 37 years of screening in Ireland. The increase in percentage of preterm births noted to have a higher incidence is 1 factor. The low iodine intake in a high proportion of pregnant women raises suspicion for iodine deficiency (potential causes noted by the authors). The investigators note that the incidence of thyroid dysgenesis was relatively stable over the study period. Although some of the increased cases might be due to some form of dyshormonogenesis, inherited in an autosomal recessive pattern, the homogeneous white population makes this unlikely. Epigenetic causes are more difficult to evaluate, but authors of studies to date do not support this mechanism as a cause for the increasing incidence.[10] McGrath et al[8] are to be congratulated for their elegant study; although some explanations are likely, a full understanding of the increasing incidence of congenital hypothyroidism remains a mystery.

ABBREVIATIONS

NBS: newborn screening
TSH: thyroid-stimulating hormone

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