Editorial

TRH Testing in Its Infancy

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In contrast to primary hypothyroidism (1:3000 to 1:4000 births), central hypothyroidism due to pituitary or hypothalamic dysfunction is rare in newborns, with a prevalence of 1:25,000 to 1:100,000 births (1, 2). Although less common, central hypothyroidism is important to recognize because it is often accompanied by other pituitary hormone deficiencies that can cause life-threatening hypoglycemia.

The hypothalamic-pituitary-thyroid axis undergoes dramatic changes in the transition from the fetal to newborn period (3). Thirty minutes after birth, newborns undergo a TSH surge to above 50 IU/liter, followed by a slow decrease to adult levels by 5–7 d of life. The TSH surge is accompanied by a rapid, 50% increase in total T_4 levels that fall to normal infant levels by 3–5 d of life. However, the intrinsic variability of a maturing thyroid axis results in normal ranges for TSH and T_4 values that vary among neonatal screening programs. Moreover, the trend toward an earlier discharge of infants and mothers from the hospital means that blood samples are being obtained earlier after birth. Considering these changes, interpreting the newborn screen must be done with sensitivity to the time of collection.

When the newborn screen identifies a patient with a low T_4 and elevated TSH level (>40 IU/liter), the diagnosis of primary hypothyroidism is certain and therapy is begun. Although less common, other combinations of abnormal thyroid function tests are possible and usually result in additional testing. For example, if a screen is collected after 4–5 d, a case of mild primary hypothyroidism may have only a slightly elevated TSH and low to low-normal T_4, mimicking central hypothyroidism. In contrast, patients with central hypothyroidism could experience a modified TSH surge followed by an increase in total T_4 over the first 48–72 h of life, enough to push their T_4 values into the normal or slightly elevated range. We know very little about the TSH surge in these patients. T_4-binding globulin deficiency, euthyroid sick syndrome, and the hypothyroxinemia of prematurity can also cause low T_4 associated with a normal TSH level. Importantly in these entities, free T_4 values are usually normal. Unfortunately, immunoassays for free T_4 are affected by low binding protein concentrations, resulting in falsely low free T_4 levels (4), which further complicates their use in infants.

To distinguish among these possibilities, additional testing is needed such as repetitive thyroid and pituitary hormone measurements and imaging of the thyroid and pituitary gland. Testing is an expensive and time-consuming approach and does not always result in a certain diagnosis. Therefore, alternative strategies may aid in the evaluation of these infants. In this issue of *JCEM*, van Tijn *et al.* (5) present their experience using the TRH stimulation test in a cohort of infants with low total T_4 and normal TSH on newborn screen (6) and in whom they later confirmed multiple pituitary hormone deficiencies and pituitary dysmorphology with stimulation testing and imaging.

After the synthesis of TRH in 1969, TRH stimulation testing was used to detect subtle states of thyroid gland dysfunction, acting as an amplifier to exaggerate underlying abnormalities in TSH secretion. As third and fourth generation TSH assays became more sensitive, however, the TRH stimulation test fell out of favor. Normal adults experience a maximum increase in serum TSH 30 min after TRH administration, and TSH levels gradually fall to basal levels by 120 min (7). In adults with pituitary or hypothalamic disease, the rise in TSH follows a different pattern. Often there is a delayed rise in TSH after TRH stimulation followed by a sustained increase. Sometimes the TSH rise is blunted or may be absent, which is more likely to be seen with pituitary disease in adults (8). Finally, an exaggerated TSH rise to TRH stimulation is occasionally noted in patients with central hypothyroidism (9, 10). This effect is thought to be due to the release of bioinactive TSH that is equally detected by immunoassays (11). These patterns have been verified in normal children and in children with hypopituitarism (12).

Experience with the TRH test in newborns is extremely limited. There are significant differences in T_4 metabolism in younger *vs.* older infants and children, which could produce different TRH stimulation test patterns in health and disease. The few available studies have used different TRH doses, collected TSH values at different times, and studied infants of various ages and clinical conditions (13–15). No other study has

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evaluated hypopituitary infants with TRH testing and collection of TSH at more than one time point. As the control group, van Tijn *et al.* (5) studied newborns with an initially abnormal newborn screen but normal second screen. These newborns experienced a TSH peak of greater than 15 IU/liter 30 min after TRH administration with a return to basal levels by 90–120 min. Although this is a normal pattern in older children and adults, it may not be appropriate to categorize this response as normal in infants, because of their initially abnormal newborn screens. As the authors concede, a small number of patients were studied, and the results need to be verified with larger numbers of normal newborns.

Importantly, newborns with confirmed pituitary dysmorphology and multiple pituitary hormone deficiencies have a serum TSH response to TRH distinctly different from the control group. Newborns with confirmed central origin of their hypothyroidism seem to have two patterns of TSH responsiveness to TRH. A subset of patients experience a slightly higher peak TSH value associated with a persistent TSH elevation. This pattern is similar to that seen in adults and children with central hypothyroidism of multiple origins. The majority of patients in this category had imaging consistent with ectopic posterior pituitary, suggesting pituitary dysplasia. In practice, this subset of patients may be difficult to distinguish from primary hypothyroidism because this response pattern is also seen in adults with primary hypothyroidism (8). The response pattern of neonates with primary hypothyroidism is unknown.

Another subset of patients had an absent or diminished response to TSH, an effect also seen in children and adults with central hypothyroidism. Interestingly, the majority of newborns with a flat TSH response to TRH had a lower incidence of multiple pituitary hormone deficiencies and a male predominance. The authors speculate that this pattern could represent a specific disorder with X-linked inheritance, and this theory will be tested as more infants are identified and studied.

But what of the clinical significance of the neonatal TRH stimulation test? After all, pediatric endocrinologists have been diagnosing central hypothyroidism and hypopituitarism for decades without the aid of the TRH stimulation test. Although this is true, the evaluation is most often pursued in infants with hypoglycemia and/or midline defects. In these instances, when clinical suspicion for hypopituitarism is high, the diagnosis can often be made without stimulation testing. Remarkably in this study, however, the abnormal newborn screen was the first sign of hypopituitarism in over 90% of the identified newborns later diagnosed with multiple pituitary hormone deficiencies; this is much higher than in previous reports (2). These babies may be a diagnostic challenge as described above, because clinical suspicion for disease is low, whereas suspicion for a false-positive screening test is high. It is in the diagnostically challenging cases that the TRH stimulation test may aid in differentiating central hypothyroidism from other diseases. Unfortunately, this is only a feasible option in Europe because TRH is unavailable in North America.

This study was performed on newborns after a very comprehensive newborn screen with low false-positive rates. Will this technique be as discriminatory in programs with higher false positive rates? It also remains to be seen whether TRH stimulation testing will be useful in the evaluation of a more diverse population of infants, such as premature infants or those with midline defects.

In summary, van Tijn *et al.* (5) have characterized the TRH stimulation test response of neonates with congenital central pituitary hormone dysfunction. In their small cohort of asymptomatic full-term neonates with persistently normal TSH levels and low free T_4 levels, the TRH stimulation test was useful in identifying neonates with true hypothalamic or pituitary disease. It remains to be seen whether this test will be applicable in cases where the thyroid function tests are more equivocal. Nevertheless, this test has potential to hasten the accurate diagnosis of pituitary disease, resulting in rapid institution of proper replacement therapy.

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