Newborn Screening for Congenital Hypothyroidism: Recommended Guidelines

During the past decade newborn screening for congenital hypothyroidism has become an important health activity in most developed countries. These screening programs have not only benefited patients and their families but also have produced new information about the epidemiology, pathophysiology, diagnosis, and treatment of thyroid disease in infancy and childhood. During this period of implementation and growth of the screening programs, a variety of issues and questions arose. Some of these have been resolved, and some have not. The point has now been reached where collaboration of the combined experiences of the North American programs can address these issues. The reader should understand that what follows reflects current opinion and may require changes when the results of the next decade of screening are reviewed.

SCREENING METHOD

Thyroxine (T₄) and Thyroid-Stimulating Hormone (TSH)

Most North American programs use a two-tiered laboratory approach. An initial T₄ measurement is followed by measurement of TSH in specimens with low T₄ values. In addition to detecting infants with primary hypothyroidism (low or low normal T₄ level with elevated TSH value; prevalence 1:3,500 to 4,500 newborns), this approach can also identify infants with thyroxine-binding globulin deficiency and some with hypothalamic-pituitary hypothyroidism (low or low normal T₄ level with normal TSH value; prevalence 1:5,000 to 10,000 and 1:50,000 to 150,000 newborns, respectively). Programs that quantify T₄ values also have the option of identifying newborns with hyperthyroxinemia (1:20,000 to 40,000 newborns).

On the other hand, this approach will miss infants who have normal T₄ values but elevated TSH values. Such infants are relatively commonplace in European programs where initial screening is done by measurement of TSH. To identify such infants, the T₄ concentration cutoff (for TSH testing) must be increased well into the normal range.

TSH

A majority of European and Japanese programs favor screening by means of primary TSH measurements, supplemented by T₄ determinations on those infants with elevated TSH values. With this approach, infants with thyroxine-binding globulin deficiency, hypo- or hyperthyroxinemia, or hypothalamic-pituitary hypothyroidism will be missed.

Until further advances are made in the state of the art of screening, the choice of the method should be based on the experience of the program, needs of the population, and availability of resources. Until T₄ and TSH determinations can be done practically on all infants, physicians should be aware of potential limitations in each method of screening for congenital hypothyroidism. Even in the absence of technical or human errors, statistical information suggests that 6% to 12% of patients with infantile hypothyroidism will have normal screening hormonal concentrations regardless of the type of approach used and can be missed by the screening programs. (Combinations of values leading to misses could be normal T₄, high TSH; normal T₄, normal TSH; low T₄, normal TSH).

Quality Assurance

The proliferation of new screening programs and the expansion of older ones has underscored the need for clear guidelines for quality assurance. With this in mind, directors of newborn screening programs and physicians are advised to become familiar with the monograph, Legal Liability and Quality...
Assurance in Newborn Screening, Lori B. Andrews, JD (ed), 1985, which can be obtained from the National Center for Education in Maternal and Child Health, Georgetown University, 38th and R St, NW, Washington, DC 20057.

THE SPECIMEN

Every newborn infant should be tested before discharge from the nursery. Results from specimens obtained within the first 24 to 48 hours of life occasionally are falsely positive for primary hypothyroidism (using TSH as the primary screen) because of the elevated levels of TSH that occur shortly after birth. However, screening before discharge is preferable to missing the diagnosis of hypothyroidism because of the lack of a clearly defined policy of responsibility for blood collection from infants discharged early. Because newborn blood specimens are used for a variety of tests and shared among different laboratories, every effort should be made to collect adequate and sufficient blood in the recommended manner (see Blood Collection on Filter Paper for Neonatal Screening Programs: Tentative Standard, NCCLS publication LA4-T, Villanova, PA, National Committee for Clinical Laboratory Standards, 1985). The recall of an infant because of an unsatisfactory specimen causes needless delay in diagnosis and treatment of a newborn with hypothyroidism. Although the testing of an unsatisfactory specimen (because of insufficient blood) can result in a false-negative TSH value, false-negative values can also result from human error in the processing of satisfactory specimens or in erroneously reporting the results.

It is highly desirable that the blood be collected between three and six days, but there will be situations when this is virtually impossible. In instances such as home births, discharge before 24 hours, or a critically ill or premature neonate, blood should be obtained by seven days after birth. When an infant is transferred to another hospital, the first hospital must indicate whether the specimen has been collected. The second hospital should obtain a specimen if there is no proof that blood was collected before the transfer.

Mothers who have undergone treatment for thyroid disorders or who have a history of a previous child with goitrous or nongoitrous congenital hypothyroidism should be identified during pregnancy to expedite the screening of the offspring.

Accurate screening results depend on good quality blood spots. Specimens that are technically unsatisfactory or contain insufficient amounts of blood should not be assayed. Blood samples should be collected on approved filter paper forms, dried at room temperature, and not subjected to excessive heat. The blood should completely saturate the filter paper and be applied to one side only. Filter paper spots should not be handled, placed on wet surfaces, or contaminated by coffee, milk, or other substances. All of the foregoing have the potential to invalidate the results regardless of the method used.

TEST RESULTS

Normal T₄ Values

The normal range of T₄ values and the cutoff level for TSH testing usually are established by the individual program. Generally, the cutoff value varies from 1.5 to 2 SD below the mean of the normal range. However, many programs have opted to use a tenth percentile cutoff.

Long-term follow-up for late-onset cases has not been reported. Programs in which second specimens are obtained (4 to 6 weeks) have indicated that 10% of hypothyroid infants with T₄ values in the normal range and elevated TSH values or with initially low TSH values were missed during initial screening. Clearly, infantile hypothyroidism can still develop even when the screening T₄ value is reported to be normal. Repeat testing should be done on serum during infancy whenever there is a clinical suspicion of hypothyroidism or when there is a family history of thyroid disease in pregnancy or familial thyroid dyshormonogenesis.

Low T₄, Elevated TSH Values

Any infant with a low T₄ and TSH value greater than 40 μU/mL of serum is considered to have primary hypothyroidism until proved otherwise. Such infants should be examined immediately and have confirmatory serum tests done to verify the diagnosis. Treatment with replacement l-thyroxine should be initiated before the results of the confirmatory tests are available. (Clinical management of infants with hypothyroidism is described below.) A small number of infants with abnormal screening values will have transient hypothyroidism as demonstrated by normal T₄ and TSH values on the confirmatory (follow-up to screening) laboratory tests. Transient hypothyroidism frequently results from intrauterine exposure to antithyroid drugs (including iodine), maternal antithyroid antibodies, or endemic iodine deficiency. Cases also have been reported in association with pseudohypoparathyroidism and prenatal or postnatal exposure to excess iodides (povidone iodine, iodinated contrast materials). The practice of using liberal quantities of iodine-containing solutions as disinfectants in newborn nurseries should be balanced against the potential for producing transient hypothyroidism.

746 CONGENITAL HYPOTHYROIDISM

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Idiopathic transient hypothyroidism and cases associated with postnatal iodine exposure are 30 times more common among premature neonates. Other features that suggest a transient condition are relatively modest elevations of TSH values (20 to 100 μU/mL), male sex, and a eutopic gland on radioisotope scanning. Because transient hypothyroidism will not be recognized in some infants, initial treatment will be similar to that in any infant with permanent infantile hypothyroidism. For this reason, it is important to determine at some later time whether or not the hypothyroidism is permanent and whether the infant in fact requires lifelong treatment (see "Assessment of Permanence of Hypothyroidism"). The one recognized exception to this is the infant with transient hypothyroidism born of a mother receiving an antithyroid drug. In virtually all such cases, the T4 and TSH values return to normal within 1 to 3 weeks after birth without treatment.

Low T4, Normal TSH Values

Infants with low T4 (approximately 2 SD below the mean of the normal range) but normal TSH values seldom have thyroid insufficiency. The low T4, normal TSH profile, seen in 3% to 5% of neonates, is associated with protein-binding disturbances such as thyroxine-binding globulin deficiency (1:5,000 to 10,000 newborns), a benign state of hypothalamic immaturity, hypothalamic-pituitary hypothyroidism (1:50,000 to 150,000 newborns), or with primary hypothyroidism in an infant with a delayed TSH response (1:100,000 newborns). Neonates who are premature or ill are found with disproportionate frequency among those with this set of laboratory values. Because there is no clear consensus with respect to follow-up, programs have elected (1) to take no further action, (2) to follow the infant until the T4 level becomes normal, (3) to request a repeat blood sample for measurement of thyroxine-binding globulin and free T4 concentrations, or (4) to perform a thyrotropin-releasing hormone test for the diagnosis of hypothalamic-pituitary hypothyroidism. In the final analysis, the responsibility for deciding which course of action to follow rests with the judgment of the attending physician. Treatment of these infants (with the exception of those with secondary hypothyroidism) with l-thyroxine is seldom justified and may do more harm than good.

Low T4, Delayed TSH Level Increase

There is now ample proof that infants with congenital hypothyroidism can be born with low T4 concentrations and normal range TSH values. Serum TSH values in these infants increase during the first few weeks of life to values characteristic of primary hypothyroidism. It is important, therefore, that screening be repeated on any infant in whom clinical signs of hypothyroidism appear. Based on experience, the prevalence of such cases is one in 50,000 to one in 100,000 newborns.

The possibility that such infants, plus those with elevated TSH values but normal T4 concentrations, would be missed on initial screening has prompted a few programs to rescreen all newborns at 2 to 4 weeks of age. Despite significant detection rates on a second screen at 2 to 6 weeks, most programs have not established a routine second screen because of: (1) the increased cost of such screening, (2) a relatively low yield of cases, (3) diversion and dilution of key personnel, (4) inability to implement new programs, (5) the prognosis of this cohort is uncertain.

CLINICAL MANAGEMENT OF NEWBORN INFANTS WITH LOW T4 AND ELEVATED TSH VALUES

Infants with low T4 and elevated TSH levels have congenital hypothyroidism until proven otherwise. Management should include:

1. Seeing the infant without delay, and if possible, evaluation by a pediatric endocrinologist.
2. Complete history, including parental thyroid status (drugs and medications) and physical examination.
3. Serum for confirmatory measurements of TSH and T4 concentrations. Serum thyroglobulin or triiodothyronine determinations may differentiate athyreotic hypothyroidism from the other types.
4. (optional). 123I-radiiodine uptake and/or scan (technetium second choice) to identify functional thyroid tissue.

There is some controversy regarding the risk to benefit ratio of early thyroid scanning of suspect infants. For those physicians who opt for imaging, the benefits can be summarized as follows: (a) If an ectopic gland is demonstrated, the permanence of thyroid disease is established. (b) The absence of thyroid gland uptake, most often associated with thyroid atrophy or hypoplasia, almost always indicates permanent hypothyroidism. However, occasionally no gland is visualized in normal infants scanned with technetium. (c) Normal scan findings (or a goiter) suggest an enzyme defect and alert the physician to the possible hereditary nature of the disorder. The presence of any enzyme defect is especially important for those families planning additional children; the scan enables the physician to arrange for genetic counseling. (d) Some infants with normal scan findings at birth may have tran-
sient disease due to blocking antibodies or drugs, and for that reason they should have a careful follow-up evaluation at 3 to 4 years of age under the conditions described in “Assessment of Permanence of Hypothyroidism.”

If a scan with \(^{123}\text{I}\) is not performed within the first few days after starting treatment, any residual thyroid function might be compromised as a consequence of TSH inhibition by the exogenous thyroid medication. However, treatment should never be delayed to obtain a satisfactory scan. If need be, the scan can be postponed until the child is of an age when treatment can be briefly interrupted without danger to the developing CNS.

Despite the arguments in favor of thyroid scanning or imaging, there remains the possibility of a slight but undefinable risk of radiation exposure. For this reason the procedure should be performed by experienced personnel with optimum equipment using the minimally recommended tracer dose. The preferable isotope for optimal scanning is \(^{123}\text{I}\), which is not available in all laboratories.

5. In addition to the other recommendations, ancillary studies such as bone maturation by standard means or by bone surface measurements may be of prognostic value in evaluation of the infant. As mentioned earlier, athyreotic infants frequently have low thyroglobulin and/or triiodothyronine concentrations.

MEDICATION

Replacement therapy should be done with \(T_4\), not triiodothyronine. The average dose of \(l\)-thyroxine at the start of treatment is 10 to 15 \(\mu\text{g}/\text{kg}\) of weight (37.5 to 50 \(\mu\text{g}/\text{d}\) for a term infant). The serum concentration of \(T_4\) (corrected for variation in thyroxine-binding globulin level) should be maintained at all times in the upper half of the normal range during the first year of life. There is evidence that those infants whose serum \(T_4\) decreases to less than 8.0 \(\mu\text{g}/\text{dL}\), accompanied by a TSH value \(>15 \mu\text{U}/\text{mL}\), for a significant period during the first year of treatment have lower IQ values than patients whose \(T_4\) levels were held constant at higher concentrations.

FOLLOW-UP

Two to four weeks after the start of treatment, clinical examination should be performed and serum obtained for TSH and \(T_4\) determinations. Physical examination and measurement of \(T_4\) and TSH should be performed 4 weeks after any change in \(l\)-thyroxine dosage. Routine clinical examination (including growth curves) should be performed, and serum submitted for measurement of \(T_4\) and TSH concentrations at 3, 6, 9, 12, 18, and 24 months of age and at each succeeding birth date and each change of dosage. Because most screening procedures are not designed to detect high levels of \(T_4\), filter paper blood specimens should not be used to monitor the absolute concentration of circulating \(T_4\) in the infant. A failure of the serum \(T_4\) concentration to increase into the upper half of the normal range by 2 to 4 weeks and/or TSH concentration to decrease to less than 20 \(\mu\text{U}/\text{mL}\) within 6 to 9 weeks after initiation of \(l\)-thyroxine should serve to alert the physician that the child may not be receiving adequate \(l\)-thyroxine regularly. At this point, careful inquiry should be made regarding compliance, dose of medication, and method of administration. When attempting to achieve the optimal level of circulating \(T_4\), physicians should always bear in mind the danger of excessive medication (eg, premature craniostenosis) and thus be prepared to monitor blood levels of \(T_4\) at close intervals.

ASSESSMENT OF PERMANENCE OF HYPOTHYROIDISM

Permanent thyroid disease can be assumed if the thyroid uptake and/or scan has revealed absent thyroid tissue, an ectopic gland, or goiter (with the previously mentioned exceptions) or if the serum TSH is seen to increase above 15 \(\mu\text{U}/\text{mL}\) after the first year, presumably because of inadequate \(T_4\) replacement.

When permanence of thyroid disease is not established, \(l\)-thyroxine administration should be discontinued sometime after the child is 3 or 4 years of age and the child not treated for 30 days. At that time, serum should be obtained for measurement of \(T_4\) and TSH levels. If the \(T_4\) and TSH concentrations remain in the normal range, euthyroidism is assumed and a diagnosis of transient hypothyroidism recorded. In this instance, however, the physician should monitor the child carefully and repeat the hormonal analysis at the slightest suspicion of relapse. If the \(T_4\) is low and the TSH elevated, permanent hypothyroidism is confirmed, and therapy is re instituted. If the results are inconclusive, careful follow-up and repeat testing will be necessary.

ADMONITION

Finally, physicians cannot and must not relinquish their clinical judgment and experience in the face of normal newborn thyroid test results. Failure of normal development can result from hypothyroidism in infants who have had normal \(T_4\) and
TSH screening results. The disorder can become manifest or acquired after the screening tests have been carried out, or rarely, the test results can be in error.

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*Pediatrics* 1987;80;745

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