Thyroid Screening in the Newborn: Utah Experience

BRUCE A. BUEHLER, M.D.*, MELVIN J. GORTATOUSKI, Ph.D.,† GLORIA SCOW, R.D.,‡ ALICIA C. HOOGASIAN,‡ and PETER C. VAN DYCK, M.D.§

*Center for Human Genetics, Department of Pediatrics, Obstetrics, and Gynecology, University of Nebraska Medical Center, Omaha, NB 68105
†Metabolic Laboratory, Department of Pediatrics, University of Utah Medical Center, Salt Lake City, UT 84132
‡Division of Maternal/Child Health, Utah Department of Health, Salt Lake City, UT 84132

ABSTRACT

Since 1979, the State Department of Health Laboratory of Utah has screened 108,256 newborn infants for hypothyroidism. The incidence of diagnosed hypothyroid children during this period was 1 per 3,800 live births. Utilizing a normal range of serum thyroid hormone levels in newborn infants of 8.0 to 26.0 μg per dl, the incidence of normal infants initially considered hypothyroid was less than one percent. A review of our three years experience is presented.

Introduction

Blood-spot screening of all newborns for thyroid deficiency began as a pilot program in 1973 in Quebec, Toronto, and Pittsburgh, PA, being incorporated into existing screening programs that had previously concentrated on the diagnosis of phenylketonuria (PKU). These initial pilot programs demonstrated the efficacy of screening all newborns of thyroid disease owing to the risk for hypothyroidism of approximately one in every 5,000 live births. In 1978 the Utah State Legislature authorized a screening program for hypothyroidism and galactosemia, which was incorporated into the existing program for PKU. This program was centralized under the State Department of Health, with a single laboratory facility. Initial screening began in January of 1979 incorporating only a few hospitals in the initial phase; over the next six months, all hospitals in the State were centralized under the state program.

The population based of 1.2 million...
people in the state of Utah accounts for approximately 41,000 births per year. Based on birth certificates and records at the State Department of Health, 98.7 percent of these births occur in the hospital while 1.3 percent are home deliveries. Utah State law requires heel-stick, blood-spot testing on all newborns, including premature infants, and a second sample is required at two to four weeks after birth. The initial testing includes assays for phenylketonuria (PKU), galactosemia, and thyroid disease. The second sample is tested for PKU only. Since the inception of this program, 108,256 initial newborn screening tests have been performed. The purpose of this paper is to summarize the data on thyroid testing accomplished during this period from 1979 to 1981.

Methods

All $T_4$ assays were done utilizing the Nichols Institute Diagnostic radioimmunoassay (RIA), double antibody test, and the results are expressed as $\mu$g per dl. This test is run on filter paper impregnated with blood obtained from heel-stick. The procedure for obtaining blood is the standard method used for PKU testing. Blood samples are obtained on the newborn infant and mailed to the State Department of Health, where they are processed daily. A single day of testing includes approximately 60 samples, tested for thyroid hormone ($T_4$) level. Utilizing an arbitrary 8.0 to 26.0 $\mu$g per dl range for normal, all samples outside this range are repeated. The repeat tests are done in duplicate and an average value obtained. Also, a thyroid stimulating hormone (TSH) level is measured on the repeat samples. The TSH is measured by the Nichols Institute Diagnostic RIA test and results are expressed as $\mu$IU per ml. The initial $T_4$, summation of the repeat $T_4$ values, and TSH are immediately forwarded to the physician. The TSH values are expressed as: less than 20, designated normal; 20 to 60, designated intermediate range; or greater than 60, designated elevated.

These results are sent by certified mail to the physician of record, and he is called at the time of mailing. A letter is sent to the family and the public health nurse recommending followup of an abnormal test. If the physician desires, a second filter paper test is performed and mailed immediately to the laboratory for repeat thyroid testing. The same procedure as previously stated is utilized, and the results are reported by phone and certified letter. If both tests show abnormal results, the physician is requested to test venous blood at an independent laboratory to quantitate $T_4$, $T_3$ uptake, and repeat a TSH. Based on this information and with consultation from the Department of Health Endocrinologist, a decision about treatment is made by the patient's physician. The final diagnosis is forwarded to the Department of Health by the treating physician.

Second filter paper tests are performed on infants at approximately two to four weeks after delivery, and these tests are sent to the State Department of Health for PKU testing only. Thyroid and galactosemia testing is done on the second filter paper sample at request of the physician.

Results

From January 29, 1979 until September 30, 1981 the State Health Department Laboratory tested 108,256 individual first tests. The recorded birth rate during 1979 was 41,078, and in 1980, it was 41,786 births. In the fiscal year 1980, all examinations including first, second, and repeat examinations totalled 236,599 tests. Only the data from 1979 and 1980 are analyzed for positive screening tests. During testing year 1979, two confirmed cases of hereditary thyroid bind-
ing globulin deficiency were reported, while nine hypothyroid patients and one patient with panhypopituitarism were identified. In 1980, no congenital thyroid binding globulin (TBG) abnormalities were reported, but there were 13 hypothyroid patients and two patients with panhypopituitarism. The positive hypothyroid screens are summarized in table I. Three categories are indicated; those patients with elevated TSH and low T4; those patients with intermediate­ly elevated TSH and low T4; and, finally, a group of patients with normal TSH and low T4. Based on this data, 62.5 percent of the patients with low T4, on initial testing, had intermediate or markedly elevated levels of TSH, while 37.5 percent of the patients had TSH values considered in the normal range.

Two patients with low T4 on initial screens were shown to have an abnormality of thyroid binding globulin (TBG). The initial T4 was 1.0, and 3.0, respectively, with their TSH value in the normal range, (less than 20 μIU per ml). The T3 uptake value was markedly elevated for both infants indicating a depressed or absent level of TBG. This was confirmed by quantitative TBG levels on their serum. The TBG values were essentially zero in both infants and the parents’ values were in the heterozygous range, verifying the diagnosis of hereditary TBG deficiency. Free T4 values on these patients were normal, and the patients did not require therapy. Both patients have been followed for two years and are neurologically normal.

Three patients with confirmed hypopituitarism were initially identified by low T4 values on the blood-spot test. In two of the infants the TSH values were in the normal range, but in one infant the initial TSH test was in the intermediate range between 20 and 60 μIU per ml value. The private physicians were alerted of the initial values and extensive laboratory testing showed panhypopituitarism in all three infants. It is interesting to note that micropenis was present in both males.

### Discussion

During the years 1979 and 1980, there were 82,864 births in the state of Utah; during this same period, 22 hypothyroid patients were ascertained. This would place the rate of hypothyroidism in Utah at one in 3,800 live births, as opposed to the national figure of one in 5,000. Most likely this is a bias of ascertainment owing to limited numbers. The calculated rate of hypopituitarism was one in 27,600 live births, and the incidence of congenital absence of thyroid binding globulin was approximately one in 41,000 live births.

Among those patients who were diagnosed with hypothyroidism, TSH values
were not always diagnostic. The patients with low T₄ and markedly elevated TSH were easily identified, but a large number of patients had borderline low T₄ in their initial screening, with TSH values in the “intermediate” to “normal” range as established by the laboratory. The majority of these patients on further testing did not have hypothyroidism, while a few patients had normal TSH and borderline T₄ values on initial screening with proven hypothyroidism.

This discrepancy raises the question of how best to approach the patient with a low T₄ value on initial screening and a normal or slightly elevated TSH. It is our experience that the most appropriate testing is a repeat T₄, TSH, and the addition of the T₃ uptake test on venous blood. Utilizing this combination of tests, it is possible to differentiate the majority of normal patients from those who have true hypothyroidism.

Uptake of T₃ (T₃U) indirectly measures the circulating level of TBG. In T₄ testing by RIA, the measured level is a summation of the bound portion attached to TBG, and free T₄. Bound T₄ accounts for approximately 99 percent of the total T₄ in serum; therefore, a change in production of thyroid hormone or a change in the circulating amount of TBG will give a low total T₄ value. Thyroid binding globulin (TBG) can be low owing to liver disease, hereditary deficiency of TBG, prematurity, or increased levels of androgens, while estrogen appears to elevate circulating TBG. In the normal full-term infant, high maternal estrogen levels elevate TBG, explaining the wide range of T₄ values for the normal newborn compared to adult values. Unfortunately, in the premature infant who may be very ill, the effect of estrogens cannot offset the immaturity of the liver and decreased TBG production; therefore, the premature infant may have a low T₄ value but be euthyroid.

Regardless of the cause, the percentage of positive tests that did not have an etiology was less than one percent. For 108,256 tests this would be as high as 1,083 tests requiring a repeat sample or TSH measurement. Numerically, this is a large number, but the repeat test in the majority of instances quickly clarified this discrepancy. Based on limited data, a reduction in this figure by a change in normal range for T₄ values might allow a true hypothyroid infant to be missed. It was felt that the range utilized and the false positive rate were justified in order not to miss a true hypothyroid infant.

The normal range of serum T₄ values by RIA in Utah is 8 μg per dl to 26 μg per dl. This value is not corrected for prematurity or for severe illness at the time of birth. To date, it has not been possible for us to derive accurate normal ranges for premature infants based on birth weight or gestational age.

The Utah program has been in effect for 2.5 years, and it is too early to determine whether or not these children diagnosed hypothyroid, will have completely normal mentation and development after adequate therapy. Preliminary data strongly suggest that the children tested to date are comparable to their normal siblings. Previous reports are very encouraging.

The treatment of a hypothyroid patient is simple and patient compliance is good. The patient is placed on synthetic T₄ (synthroid), and serum levels of total T₄ are adjusted monthly until stable. In our program, the initial dosage for full-term newborns was 0.025 mg of synthroid with the majority of infants requiring 0.050 mg by the age of one year. In premature infants with birth weights less than 2,500 grams, initial dosage was 0.0125 mg of synthroid daily. This dosage is then adjusted, and most premature infants require 0.025 mg daily by one year of age.
In those patients with hereditary absence of TBG, no therapy was required and their free T₄ measurements remained within normal limits. Finally, in patients with hypopituitarism, steroid replacement was the initial therapy. After 24 hours of steroid therapy, the patients were begun on synthroid at the same dosage schedules indicated for hypothyroid infants. These patients required close follow-up to maintain adequate steroid levels, but thyroid management was equivalent to normal infants.

Newborn screening for thyroid disease is an inexpensive, efficacious way to prevent the devastating damage of untreated (hypothyroidism cretinism) in children. With an estimated rate of one per 3,800 live births having hypothyroidism, 53 children in Utah, alone, should be identified in the next five years.

References