

Frequency and Necessity of Thyroid Function Tests in Neonates and Infants With Congenital Hypothyroidism

Maria G. Vogiatzi, MD, and John L. Kirkland, MD

ABSTRACT. *Objective.* The American Academy of Pediatrics recommends frequent thyroid function tests in infants and children with congenital hypothyroidism (CH). Data supporting the recommended frequency are lacking. This review was conducted to assess the validity of these recommendations.

Methods. The thyroxine (T4) and thyroid-stimulating hormone (TSH) levels of 50 neonates diagnosed between 1988 to 1993 were reviewed to assess the length of time on a specific dose of levothyroxine.

Results. 1) Changes in the dose of levothyroxine occurred 35 times during the first year of life for the 39 children treated with .025 mg/day, five times during the first year of life for the 9 children treated with .0375 mg/day, and three times during the first year of life for the 2 children treated with .050 mg/day. 2) These dose changes occurred at varying time intervals. 3) The T4 and TSH levels obtained at visits requiring dose changes were statistically different from the T4 and TSH levels obtained at the previous two visits. The T4 and TSH levels at the two visits before the change in dosage did not differ statistically.

Conclusions. 1) An initial levothyroxine dose of .0375 mg/day requires fewer dose changes than a dose of .025 mg/day. 2) A lack of statistical change in T4 or TSH levels obtained at visits before the change-in-dose visit and the variable time span between dose changes necessitate frequent monitoring regardless of the dose of levothyroxine, the previous T4 or TSH levels, or the length of time at a specific dose. 3) These data support the recommendations of the American Academy of Pediatrics regarding the frequency of thyroid function studies during the first 2 years of life. *Pediatrics* 1997;100(3). URL: <http://www.pediatrics.org/cgi/content/full/100/3/e6>; *levothyroxine, congenital hypothyroidism, American Academy of Pediatrics, T4 levels, TSH levels.*

ABBREVIATIONS. CH, congenital hypothyroidism; T4, thyroxine; AAP, American Academy of Pediatrics; TSH, thyroid-stimulating hormone.

Appropriate treatment of congenital hypothyroidism (CH) prevents severe mental retardation.^{1,2} Early treatment and normalization of thyroxine (T4) values, as well as constant T4 concentrations in the upper half of the normal range (more than 10 $\mu\text{g}/\text{dL}$) during the first 3 years, are associ-

ated with improved intellectual outcome.^{1,3-5} The importance of treatment prompted the American Academy of Pediatrics (AAP) to issue recommendations twice since 1987.^{6,7} In 1993, the AAP published the following schedule for obtaining laboratory evaluations:

1. At 2 and 4 weeks after the initiation of L-thyroxine treatment.
2. Every 1 to 2 months during the first year of life.
3. Every 2 to 3 months between 1 and 3 years of age.
4. Every 3 to 12 months thereafter until growth is completed.
5. At more frequent intervals when compliance is questioned or abnormal values are obtained.

These laboratory recommendations appear indicated but support of medical necessity is unavailable. In the current health care environment, third-party payors design yearly reimbursement plans to pay physicians and hospitals a per capita fee, ie, capitation fee. Preparations for capitation in our Pediatric Endocrine Clinic compelled justification of these recommendations because capitation invokes financial penalties for unnecessary laboratory tests. The current study reviews, retrospectively, the number and timing of the dose changes in levothyroxine. The T4 and thyroid-stimulating hormone (TSH) levels before the change were analyzed to determine the predictability for suggesting a change in dose.

METHODS

The medical charts of 57 full-term children with CH diagnosed between 1988 and 1993 and followed in the Pediatric Endocrine Clinic at Texas Children's Hospital were reviewed. Seven children with poor compliance were excluded. Initial amounts of replacement with levothyroxine varied among the five physician members of the Pediatric Endocrine Clinic, according to their usual clinical practice. The initial amounts were .025, .0375, and .050 mg daily. The children were followed at 2 month intervals during the first year and at 3-month intervals thereafter. T4 and TSH levels were obtained at each visit. The doses were adjusted to maintain the T4 levels in the upper half of normal range (10 to 14 $\mu\text{g}/\text{dL}$) according to AAP recommendations. A dose change to keep the T4 levels in the above range could then be used as a marker to justify that the laboratory studies were mandatory. TSH levels remained elevated in some infants during the first months of life and were not considered as criteria for changing a dose. In the remaining cases, TSH levels were maintained as close to normal as possible ($<5 \mu\text{IU}/\text{mL}$).

T4 was measured by fluorescence polarization immunoassay technology. The sensitivity of the assay was .7 $\mu\text{g}/\text{dL}$. TSH was measured by the microparticle enzyme immunoassay technology with sensitivity .03 $\mu\text{IU}/\text{mL}$. The results are expressed as the mean \pm the standard deviation (SD) unless otherwise indicated. Statistical analysis was performed with analysis of variance, and P values are expressed.

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RESULTS

The first Pediatric Endocrine Clinic visit and initiation of levothyroxine therapy occurred at 20 ± 5.6 days of age. The administered dose was .025 mg/day in 39 children, .0375 mg/day in 9 children, and .050 mg/day in 2 children. Pretreatment levels of T4 and TSH at the start of treatment were $3.6 \pm 2.6 \mu\text{g/dL}$ and $380 \pm 353 \mu\text{IU/mL}$, respectively.

The results are presented in two sections. The first compares the effect of the initial dose of levothyroxine on T4 levels, whereas the second compares the dose effect on TSH levels.

Dose of Levothyroxine and T4 Levels

Initial Dose of .025 mg/Day

The initial dose of .025 mg/day was administered in 39 children. Birth weight was $3.75 \pm .53$ kg, with a range of 2.7 to 4.9 kg. The levothyroxine dose per kilogram was $6.6 \pm 1.26 \mu\text{g/day}$. These children required a dose adjustment after 6.8 ± 5 months, with a range of 1 to 19 months. A total of 89% (35 children) required an increase to .0375 mg/day during the first year (see Table 1). Ten of these children required an additional increase to .050 mg/day, and six required an increase to .0625 mg/day during the first year of life. Additional changes occurred during the second year at frequent intervals. Fig 1A reveals the change in the T4 levels at the time of dose change (0 visit) and at the two previous visits (-1 and -2 visits). Levels at visits 0 were lower than those at visits -1 and -2 ($P < .001$). No difference existed in levels at visits -1 and -2 ($P > .05$).

The next dose of levothyroxine, .0375 mg/day, lasted for 12.5 ± 10 months, with a range of 1.5 to 33 months (Table). Changes of dose occurred at frequent intervals thereafter. The data was analyzed to determine whether differences existed between the T4 levels at the visits before the change. The T4 levels at the time of the change differed statistically ($P < .001$) from the previous visit, but the T4 levels at the two previous visits did not differ from each other ($P > .05$) (data not shown).

The length of treatment on the subsequent dose of

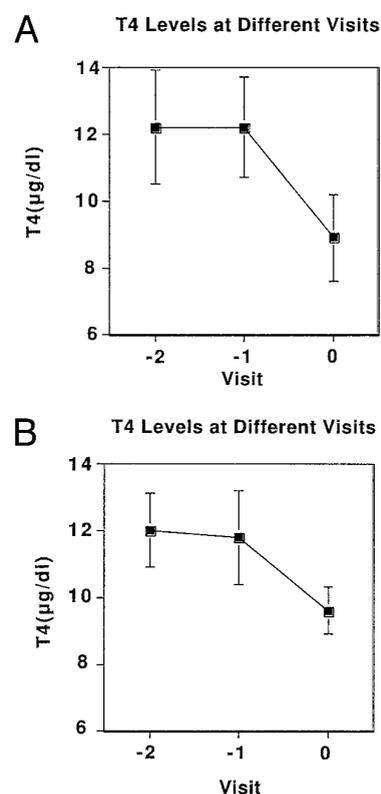


Fig 1. The T4 levels at different visits. The T4 levels were calculated as the mean \pm SD at the time of dose change, the 0 visit. The mean T4 levels were calculated as above for the two visits before the dose change was made, the -1 and -2 visits. A, mean and SD T4 levels at the initial dose of .025 mg/day, and B, T4 levels at the initial dose of .0375 mg/day. The mean T4 level at the 0 visit differs significantly ($P < .001$) from that for the two previous visits (-1 and -2 visits). The T4 levels at the two previous visits (-1 and -2 visits) did not differ significantly ($P > .05$) from each other.

levothyroxine, .050 mg/day, was 24.8 ± 16 months, range, 7 to 64 months. Changes of dose occurred at frequent intervals as with the two previous doses. The T4 levels at the time of the change differed statistically ($P < .001$) from the previous visit. The T4 levels at the two previous visits did not differ from each other ($P > .05$, data not shown).

TABLE 1. Time of Dose Changes With Initial and Subsequent Doses of Levothyroxine

	Dose				
	0.025 mg/Day as Initial Dose			0.0375 mg/Day as Initial Dose	
	0.025	0.0375	0.050	0.0375	0.050
Number of patients	39	19	33	9	5
Length of treatment					
Mean \pm SD (months)	6.8 ± 5	12.5 ± 10	24.8 ± 16	13.3 ± 8	20.5 ± 10
Range (months)	1-19	1.5-33	7-64	1-30	8-43
Number of patients requiring a dose change during					
2-Mo follow-up	7	2	0	1	0
4-Mo follow-up	7	3	0	0	0
6-Mo follow-up	6	1	0	0	0
9-Mo follow-up	12	3	5	1	0
12-Mo follow-up	3	1	1	3	1
15-Mo follow-up	1	2	2	0	0
18-Mo follow-up	1	2	1	1	0
24-Mo follow-up	2	3	3	1	1

Initial Dose of .0375 mg/Day

Nine children received .0375 mg/day of levothyroxine as an initial dose. Birth weight was 3.72 ± 0.59 kg, with a range of 2.29 to 4.2 kg, so that the dose per kilogram was 10 ± 2.3 $\mu\text{g}/\text{day}$. In these children, a dose change was required in 13.3 ± 8 months, with a range of 1 to 30 months. A total of 55% (5 children) required an increase in their dose during the first 12 months (see Table). As with the other doses, changes occurred at varying intervals during the first 2 years of life. Fig 1B demonstrates the changes that occurred in the T4 levels at the time of dose change (0 visit) and in the T4 levels at the two previous visits. The T4 levels at the time of change differed statistically ($P < .001$) from the previous T4 levels, but no statistically significant difference existed in the two previous levels ($P > .05$). The subsequent dose of .050 mg/day in five children lasted 20.5 ± 10 months, but the small number precluded additional analysis.

Initial Dose of .050 mg/Day

Two children received .050 mg/day of levothyroxine; the birth weights were 3.39 and 3.1 kg and the doses per kilogram were 16.1 and 14.7 $\mu\text{g}/\text{day}$. Both infants required a reduction in their doses to .0375 mg/day in the first month, and one required an additional reduction to .025 mg/day (data not shown).

Dose of Levothyroxine and TSH Levels

TSH Concentrations

TSH levels of neonates treated initially with .025 and .0375 mg/day at the time of change (visit 0) and at the two previous visits (visits -1 and -2) are presented in Fig 2. TSH concentrations were significantly higher at visit 0 (16.5 ± 11.8 $\mu\text{IU}/\text{mL}$) compared with previous visits ($P < .001$), whereas no differences were observed between -1 and -2 visits (5.2 ± 2.5 and 4.59 ± 4.55 $\mu\text{IU}/\text{mL}$, respectively). Similar results were observed when TSH levels of

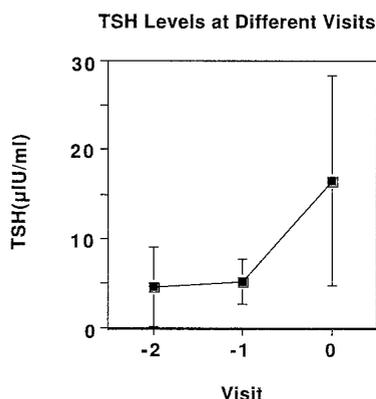


Fig 2. The TSH levels at different visits. The TSH levels were calculated as the mean \pm SD at the time of dose change, the 0 visit. The TSH levels were calculated as above for the two visits before the dose change was made, the -1 and -2 visits. Figure 2 shows the mean and SD TSH level at the initial doses of .025 and .0375 mg/day. The TSH level at the 0 visit differs significantly ($P < .001$) from the values for the two previous visits (-1 and -2 visits). The TSH levels at the two previous visits (-1 and -2 visits) did not differ significantly ($P > .05$) from each other.

neonates receiving either .025 or .0375 mg/day were analyzed separately (data not shown).

Eleven children, eight treated initially with .025 mg/day and three with .0375 mg/day, had elevated TSH levels despite appropriately high T4 values during the first year of life. TSH concentrations remained elevated for 12 ± 9.9 months, with a range of 4 to 40 months. The TSH values of these neonates and infants were excluded from the above analysis.

DISCUSSION

Laboratory assessment of children with CH allows appropriate dose adjustments of levothyroxine. The frequency of laboratory assessment must ensure that abnormal thyroid function levels are corrected immediately. The AAP has promulgated standards recommending T4 and TSH levels at 1- to 3-month intervals for the first 3 years of life. However, capitation payments require prospective evaluation of medical practice guidelines, because financial penalties exist for unnecessary laboratory studies.

This review demonstrates that changes in the dose of levothyroxine depend on the initial dose. A total of 55% of the children treated with .0375 mg/day of levothyroxine as an initial dose required a dose change, whereas 89 percent of children treated with .025 mg/day required a dose change within the first 12 months. Ten of the latter group required a subsequent change to .050 mg/day during the first year. This difference can be explained by the higher dose per kilogram of body weight in the group receiving .0375 mg/day. However, the dose of .0375 mg/day lacks any advantage over the other for capitation purposes, because the dose changes at any dose were varying and unpredictable.

The T4 levels obtained at the two previous visits before a dose change did not indicate a trend that would signify an impending dose change. Figure 1A (initial dose of .025 mg/day) indicates T4 levels of 12.2 ± 1.5 $\mu\text{g}/\text{dL}$ one visit before the change and T4 levels of 12.2 ± 1.7 $\mu\text{g}/\text{dL}$ two visits before the change ($P > .05$). Figure 1B (initial dose of .0375 mg/day) indicates levels of 11.8 ± 1.4 $\mu\text{g}/\text{dL}$ one visit before the change and levels of 12.0 ± 1.1 $\mu\text{g}/\text{dL}$ two visits before the dose change. Analysis of subsequent doses revealed a similar pattern. Analysis of TSH levels revealed a similar pattern as well. These data indicate that previous levels of T4 or TSH do not indicate a predictable change, pattern, or trend that can be recognized to indicate that a dose change is likely at a future visit.

The length of time at a specific dose was variable. The initial dose of .025 mg/day had a range of 1 to 19 months, and the initial dose of .0375 mg/day had a range of 1 to 30 months. Dose changes made after the initial changes revealed a similar variation.

The decision to use .0375 or .050 mg/day as an initial dose in children with CH remains controversial. Doses of 10 to 15 $\mu\text{g}/\text{kg}/\text{day}$, favoring .050 mg/day, reportedly produce improved intellectual outcome but poorer visual motor and numerical processing skills, as well as temperamental difficulties.^{3-5,8-10} Another report suggests that the initial T4 levels, but not the amount of replacement therapy,

determine the intellectual outcome.¹¹ In the present study, the number of children treated with .050 mg/day as an initial dose was inadequate to support any conclusions, but laboratory assessment should be frequent. The infants treated initially with .050 mg/day of levothyroxine soon required a reduction to either .0375 or .025 mg/day. One would expect, therefore, that these infants would require the same careful monitoring of thyroid tests, even more so during the first 2 months if iatrogenic hyperthyroidism is to be avoided.

Limitation of this study includes its retrospective design. No neuropsychologic assessment of the treated neonates and infants was obtained. This study, however, supports guidelines for laboratory tests for today's practicing physician. These guidelines will ensure adequate thyroxine replacement based on previous reports of improved neurodevelopmental outcome with early, aggressive thyroid replacement.

Our data support the recommendations made by the AAP for testing of thyroid function in children with CH for the first 2 years of life. The dose of levothyroxine, length of time on that dose, and the previous T4 or TSH levels do not indicate when a dose change will be required. Recent changes in the health care industry include attempts to reduce medical costs through capitation payments. Financial survivability under capitation requires prospective evaluation, planning, and diligent monitoring of all aspects of medical practice, including laboratory testing.¹² Frequent thyroid function testing when most results are normal may suggest unnecessary laboratory studies. Therefore, the use of capitation pay-

ments for children with CH must account for the frequency of recommended laboratory studies.

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