Relationship of Etiology to Treatment in Congenital Hypothyroidism

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ABSTRACT

We examined the patterns of TSH, T4, and treatment schedules from diagnosis to 4 yr of age in 125 children (50 males and 75 females) with congenital hypothyroidism (CH). Subjects were divided into 3 groups based on their thyroid scans: 1) athyreosis (n = 31), 2) dysgenesis (n = 54; 49 lingual and 5 hypoplastic), and 3) dyshormonogenesis (n = 40). Follow-up evaluation was carried out at 2–4 wk and 3, 6, 9, 12, 24, 36, and 48 months of age. Median gestational age, age at onset of therapy, and starting L-T4 dose were similar in the three groups. In infants with athyreosis median screening TSH levels were higher (P < 0.02) and confirmatory T4 levels were lower than in the other two groups (P < 0.01 vs. dysgenetic; P < 0.05 vs. dyshormonogenetic CH). During the first 6 months of therapy, mean TSH levels were highest in the athyrotic group, intermediate in the dysgenetic group, and lowest in the dyshormonogenetic group. In children with athyreosis, TSH levels normalized by 12 months of age. At 12 months dysgenetic patients had the highest TSH levels (P < 0.05). During the entire study period, TSH levels were lowest in patients with dyshormonogenesis (except at 48 months) and normalized earlier. Mean T4 levels normalized by 2–4 weeks in all groups. At 3 and 6 months, the percentage of patients who required dose changes was highest in the athyrotic group, and at 12 months it was highest in the dysgenetic group. The athyrotic group received the highest dose of L-T4, and dyshormonogenetic group received the lowest dose. We conclude that treatment and follow-up schedules for CH may differ in the three etiological categories based on the different hormonal patterns and responses to therapy. Children with athyreosis need close monitoring particularly early in life, whereas those with dysgenesis and dyshormonogenesis require more attention later in life. (J Clin Endocrinol Metab 86: 186–191, 2001)

EARLY DIAGNOSIS and treatment are crucial to prevent mental retardation in congenital hypothyroidism (CH). Although neonatal screening programs have been extremely successful in the elimination of severe mental retardation related to CH (1–6), subtle intellectual impairment may be detectable even in children treated very early in life (2, 7–10). It has been proposed that the severity of CH has a threshold effect on brain development, probably determined prenatally (7–9). However, some studies suggest that intellectual impairment in children with severe hypothyroidism, determined by low circulating levels of T4 and marked retardation of skeletal maturation at diagnosis, can be minimized by treating more promptly after birth and by using a higher initial dose of levothyroxine (L-T4) (7, 11–16). Despite this markedly improved outcome with early initiation of treatment, better treatment protocols are still needed to eliminate subtle persisting neuropsychological impairment, particularly among those with the most severe hypothyroidism.

The etiology of CH may also play an important role in determining both the disease severity at diagnosis as well as its outcome (15). In addition, factors such as lower TSH, higher T4, and greater delay in skeletal maturation may be related to etiology. However, only one previous study has assessed L-T4 therapy longitudinally in children according to the etiology of their hypothyroidism (15). In that study the follow-up period was only 1 yr, and the numbers of subjects with dyshormonogenesis and dysgenesis were small (9 and 13 children, respectively).

The purpose of this study was to evaluate thyroid hormone levels and patterns of L-T4 dose adjustment in a large cohort of children with CH followed from diagnosis to 4 yr of age according to their etiology determined by radionuclide imaging studies. We hypothesized that TSH and T4 concentrations, L-T4 dose requirements, and frequency of dose adjustments in these subjects would differ according to the etiology of the hypothyroidism. We also assumed that if differences exist, these would help determine specific follow-up schedules and dosing levels appropriate for each diagnostic group.

Subjects and Methods

The study population consisted of 125 infants with CH (50 males and 75 females) who were diagnosed by TSH screening in Ontario, Canada (2), between 1985 and 1995 and were referred for treatment and follow-up at the Hospital for Sick Children (Toronto, Canada). In all infants, elevated screening TSH concentrations were confirmed by measurement of serum concentrations of TSH and T4 at a median age of 12 days (Table 1). Immediately after confirming the diagnosis, L-T4 therapy was started at doses of 25, 37.5, or 50 μg/d to provide approximately 10 μg/kg/day. As part of the routine evaluation of CH at the Hospital for Sick Children, all infants underwent radionuclide imaging studies at the time of confirmation of the diagnosis to define the etiology. On the basis of the technetium 99m thyroid scan results, the CH subjects were divided into 3 groups. In group 1 athyreosis was diagnosed in infants whose thyroid scans did not show any radionuclide uptake. This group consisted of 31 infants (19 females and 12 males). One subject in this group
TABLE 1. Characteristics and hormone levels in 125 patients with congenital hypothyroidism at screening and onset of therapy

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Sex (F/M)</th>
<th>Gestation (weeks)</th>
<th>Age (days)</th>
<th>Screening TSH (mU/L)</th>
<th>Confirmatory TSH (mU/L)</th>
<th>T₄ (nmol/L)</th>
<th>Dose (µg/kg)</th>
</tr>
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<tbody>
<tr>
<td>Athyrogenesis</td>
<td>31</td>
<td>19/12</td>
<td>40 (37–42)</td>
<td>12 (3−25)</td>
<td>122₃ (63–401)</td>
<td>50 (2–1396)</td>
<td>18.5 (10–164)</td>
<td>9.4 (7–14)</td>
</tr>
<tr>
<td>Dysgenesis (dg)</td>
<td>54</td>
<td>42/12</td>
<td>40 (36–43.5)</td>
<td>12 (8–145)</td>
<td>100 (20–250)</td>
<td>50 (28–667)</td>
<td>77 (8–242)</td>
<td>9.2 (4–13)</td>
</tr>
<tr>
<td>Dyshormonogenesis (dhg)</td>
<td>40</td>
<td>14/26</td>
<td>40 (36–42)</td>
<td>13 (7–130)</td>
<td>100 (20–250)</td>
<td>50 (8–609)</td>
<td>55.5 (10–212)</td>
<td>9.3 (5–13)</td>
</tr>
</tbody>
</table>

The values are expressed as median and range.

a One subject detected due to clinical signs and symptoms.
b P < 0.01 vs. dg; P < 0.02 vs. dhg.
c P < 0.01 vs. dg; P < 0.05 vs. dhg.

had no visible thyroid tissue on thyroid scan, but had a confirmatory TSH concentration of only 2 mU/L. The reason for this remains uncertain, although the subsequent course (rapid rise in TSH on stopping l-T₄ therapy and the need for frequent dose changes within the first year of life) confirmed the diagnosis of CH. In group 2 dysgenesis was diagnosed in infants whose thyroid scans demonstrated uptake of the tracer at the base of the tongue (lingual; n = 49 patients) or indicated either small (n = 2) or hemiagenetic (n = 3) glands on uptake. This group consisted of 54 patients (42 females and 12 males). In group 3 dysshormonogenesis was diagnosed in infants whose thyroid gland was enlarged and showed avid uptake of the tracer by a normally located and shaped thyroid gland (n = 33). Four additional infants (2 pairs of brothers), who demonstrated no significant technetium 99m uptake were assigned to the dysshormonogenic group. In 1 pair there was a bilobular thyroid gland in the normal location on ultrasound, and in the other pair, 1 had a small thyroid gland with poor uptake of the tracer. They were, therefore, considered to have a trapping defect. In 3 additional patients, thyroid scans were not performed because their older brothers had documented goitrous hypothyroidism, as indicated by a thyroid scan showing an enlarged gland with increased uptake, or other family members presented with visible goiter. The dysshormonogenic group, therefore, consisted of a total of 40 infants (14 females and 26 males).

Subjects were included only if their initial and follow-up evaluations were carried out at this hospital for a period of at least 4 yr. The first evaluation was performed 2–4 weeks after the initiation of therapy, and subsequent evaluations occurred at 3, 6, 9, 12, 18, 24, 36, and 48 months of age. When needed, additional visits were scheduled. The dosage adjustments at each visit were made according to clinical and biochemical data. The dose was adjusted when the TSH concentration was more than 7 mU/L or less than 0.1 mU/L. In patients with hyperthyroxinemia associated with decreasing but still elevated TSH values, no additional dose changes were made. In general, the dose was adjusted by 12.5-µg increments (e.g. 37.5, 50, 62.5, and 75 µg/day) based on the size of the available pills. As the number of patients who needed a decrease in l-T₄ dose during follow-up visits was negligible, the term dose change throughout this report refers to a dose increase. In those patients who remained on small doses (25–50 µg/day) of l-T₄ until the age of 3–4 yr, l-T₄ therapy was withdrawn for 3–6 weeks to reassess the need for permanent replacement therapy (17).

In many infants, the screening TSH results were reported by the provincial health laboratory as more than 100 or 250 mU/L and the confirmatory TSH as more than 50 or 60 mU/L. For the purposes of data analysis, these results were considered as 100, 250, 50, and 60 mU/L, respectively. Similarly, confirmatory T₄ results reported as less than 10 nmol/L at diagnosis were considered as 10 nmol/L. Confirmatory TSH and T₄ levels were determined in the Department of Pediatric Laboratory Medicine at the Hospital for Sick Children, using a sensitive third generation TSH immunoassay and homogeneous latex agglutination, respectively (Immuno 1 System, Bayer Corp.). The normal reference ranges for TSH and T₄ concentrations did not change throughout the study period.

Statistical analysis

The data were analyzed as follows. Repeated measures ANOVAs were performed to determine the patterns of T₄ and TSH concentrations in the three CH groups over the 4-yr study period. Pearson correlation coefficients were used to assess the relationship between l-T₄ dose and therapeutic outcome. χ² analysis (goodness of fit test) was used to evaluate the proportion of subjects requiring dose adjustments at each

Results

The characteristics of the patients and their hormonal results at screening and onset of therapy are shown in Table 1. A female preponderance was evident in the athyreotic and dysgenetic groups (61% and 77%, respectively), whereas only 35% of the patients with dysshormonogenesis were female (P < 0.001). The median gestational age, age at onset of therapy, and starting dose of l-T₄, expressed as micrograms per kg, were similar in all three groups.

Screening and confirmatory TSH and T₄

Screening TSH values were higher in infants with athyreosis than in those with either dysgenetic or dysshormonogenetic CH (P < 0.01 and P < 0.02, respectively; Table 1). Median confirmatory T₄ levels were lowest in infants with athyreosis compared with infants with dysgenesis and dysshormonogenesis (P < 0.01 and P < 0.05 respectively; Table 1). The percentage of infants reported to have screening TSH levels higher than 100 or 250 mU/L was also significantly higher in athyreotic infants (55%) than in infants with dysgenic or dysshormonogenetic CH (29% of the infants in both groups; P < 0.05). Similarly, the percentage of patients reported to have T₄ concentrations less than 10 nmol/L was higher in the athyreotic group than in the other two etiological groups (30% vs. 4 and 5%, respectively; P < 0.001).

Follow-up results

The pattern of TSH concentrations throughout the 48-month follow-up period varied greatly among the three groups (Table 2). During the first 3 months of therapy, mean TSH levels were consistently higher in the athyreotic group than in either the dysgenic or dysshormonogenetic groups. The differences were highly significant at 2–4 weeks and 3 months. At the 6-month follow-up, the mean TSH concentration in the athyreotic group was still the highest, although a significant difference was now found only between the athyreotic and dysshormonogenetic groups (P < 0.05). The higher TSH levels during the first 6 months in athyreotic patients also corresponded to the number and percentage of infants who required an increase in l-T₄ dose (Fig. 1). Mean TSH levels normalized by 12 months of age in athyreotic subjects, whereas patients with dysgenetic CH had an increase in TSH concentrations at 12 months compared with
the other two groups (Table 2) and required a dose increase (Fig. 1). At 18 months, the mean TSH levels in the athyrotic group increased again compared with those in the other two groups, although the difference did not attain statistical significance. Thereafter, the mean TSH levels fluctuated between normal (24 and 36 months) to slightly elevated levels (48 months), and during this period no significant differences were observed between the groups. In patients with dyshormonogenesis, the mean TSH levels normalized earlier (9 months) despite the fact they received the lowest doses of \( l-T_4 \) and required the fewest dose increases. In addition, their mean TSH values remained lowest throughout the study period except at 48 months.

In all groups, mean \( T_4 \) levels normalized rapidly and remained consistently within normal limits throughout the study period (Table 2).

Levothyroxine dose

During the entire study period, the athyrotic group received the highest dose of \( l-T_4 \), and the subjects with dyshormonogenesis received the lowest dose (Table 3). By 12 months of age, the doses per kg BW had decreased by about 40% from the initial doses. The mean \( T_4 \) levels in the dyshormonogenetic group remained lowest throughout the study period (Table 2).

**TABLE 2.** TSH and \( T_4 \) values in 125 children with congenital hypothyroidism during 4 yr

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>2–4 weeks</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
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<td>157</td>
<td>25.7</td>
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<td>147</td>
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<td>152</td>
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<td>(0.1–70.8)</td>
<td>(95–252)</td>
<td>(0.1–5)</td>
<td>(95–232)</td>
<td>(0.1–13.7)</td>
<td>(87–208)</td>
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<td>1.8</td>
<td>152</td>
<td>1.1</td>
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<td>5</td>
<td>1.4</td>
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<td></td>
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<td>(95–200)</td>
<td>(95–232)</td>
<td>(0.1–13.7)</td>
<td>(87–208)</td>
<td>(0.1–28.0)</td>
<td>(106–195)</td>
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<td>(0.1–127.3)</td>
<td>(43–291)</td>
<td>(0.1–60)</td>
<td>(83–223)</td>
<td>(0.1–15.1)</td>
<td>(85–287)</td>
<td>(0.1–50)</td>
<td>(86–187)</td>
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<tr>
<td>Dyshormonogenesis</td>
<td>40</td>
<td>2.7</td>
<td>170</td>
<td>1.3</td>
<td>160</td>
<td>2.2</td>
<td>145</td>
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<td>(0.1–50)</td>
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<td>131</td>
<td>3.8</td>
<td>125</td>
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</table>

The values are expressed as median (range). Units for TSH and \( T_4 \) are milliunits per L, nanomoles per L, respectively.

\( * P < 0.005 \) vs. \( dg \); \( \dagger P < 0.001 \) vs. \( dg \).
\( \ddagger P < 0.05 \) vs. \( dg \).
\( \| P < 0.01 \) vs. \( athyrosis \).
\( _P P < 0.05 \) vs. \( athyrosis \).
between the dyshormonogenetic and the other two CH groups (Table 3).

At follow-up, the percentage of patients in the three etiological groups who required dose changes reflected the hormonal status of each group at that time (Fig. 1). At the 3 and 6 months visits, respectively, 52% and 48% of subjects with athyreosis required dose changes, whereas in the dyshormonogenetic group the corresponding figures were 13% and 22%. The percentage of infants with dysgenetic CH who needed a dose change at 3 and 6 months was intermediate compared with those in the other two groups (19% and 31%). Although most patients who needed dose changes at 3 and 6 months visits were in the athyrotic group, the majority requiring a dose change at 12 months were those with dysgenetic CH (37% vs. 16% and 18%; Fig. 1). Subjects with dyshormonogenesis had the lowest percentage of dose changes throughout the study period (range, 2.5–22.5%; Fig. 1). χ² analysis showed significant group differences in the percentage of subjects needing a dose change at 2–4 weeks (P < 0.05), 3 months (P < 0.01), and 12 months (P < 0.05).

To assess the function of the hypothalamic-pituitary-thyroid axis, we performed correlations between current TSH concentration and l-T₄ dose at the previous follow-up visit. We found significant negative correlations in the athyrotic group, but not in the other two groups: 2–4 weeks, r = −0.46; P < 0.02; 3 months, r = −0.43; P < 0.05; 9 months, r = −0.4; P < 0.05; and 12 months, r = −0.54; P < 0.01. In fact, in the dyshormonogenetic group, we found a significant positive correlation between TSH levels and the dose at previous follow-up visit at 9 and 12 months only (r = 0.40 and r = 0.43, respectively; P < 0.05), reflecting the low levels of both TSH and l-T₄ dose during these visits.

**TSH and T₄ correlations at diagnosis and follow-up**

In all three groups, there was a significant inverse correlation between TSH and T₄ concentrations at most time intervals after initiation of therapy (r = −0.31 to −0.63; P < 0.05). However, there was no correlation between TSH and T₄ concentrations in the athyrotic group at the 2–4 week evaluation.

**Discussion**

Screening for and early management of CH have eliminated this as a cause of severe mental retardation (1–6). Nevertheless, several studies show subtle neuropsychological disturbances in some children with CH who received early and effective therapy (2, 7–10). The severity of the hypothyroidism at initiation of therapy has been the most consistent predictor of these subtle abnormalities. In general, where the etiology of CH was determined, those with athyreosis had the most severe outcome (7, 9, 14, 18). There are limited data available on patterns of hormonal concentrations for T₄ and TSH in children with different etiologies of CH. This longitudinal study of 125 children with CH diagnosed between 1985–1995 revealed distinct hormonal patterns and unique responses to therapy in the athyrotic, dysgenetic, and dyshormonogenetic groups. This is the first study to follow this large a cohort of subjects for such an extended period of time and the first to chart the course of hormonal changes in relation to dose changes.

Despite rapid normalization of mean T₄ levels in all three groups, mean TSH levels at screening and during the first 6 months of follow-up were consistently higher in those with athyreosis than in those with dysgenetic or dyshormonogenetic etiologies. The athyrotic group also had the lowest mean T₄ levels at diagnosis and 3 months of age. At 1 yr of age, we found that the mean TSH levels of dysgenetic CH patients became significantly higher than those in the other groups. By 24 month of age and at all subsequent visits, the dyshormonogenetic group showed significantly lower total T₄ levels than the other two groups.

Previous studies in which the disease severity was related to etiological category either were not longitudinal (18–21) or were limited by their short duration of follow-up and small cohort size (15). As in this report, most of these studies found the lowest screening and pretreatment T₄ levels in the athyrotic (agenesis) group (18–21). One study reported significantly higher pretreatment T₄ levels in those with a dysgenetic hypothyroidism than in those with athyreosis or dyshormonogenesis (21). The latter study included only 11 infants with athyreosis, 2 with dyshormonogenesis, and 28 with dysgenetic thyroid glands. This is not the usual etiological distribution and may reflect sampling bias.

Differences between TSH concentrations determined at screening and diagnosis in the three etiological groups have been even less consistent. Only 1 study reported that the screening TSH level was highest in the athyrotic group (20). Another reported that TSH concentrations did not significantly differ from those in the other 2 groups; however, only 13 patients with dysgenetic thyroids and 9 with dyshormonogenesis were included (15).

**Follow-up data and etiology: dose relationships**

Our study demonstrates that a clear difference in the severity of CH depends on etiology not just at diagnosis but...
also during follow-up to age 4 yr. During the first 6 months of life, the athyrotic group was the most severely affected. The mean TSH concentrations during this period were highest in the athyrotic group, intermediate in the dysgenetic group, and lowest in those with dyshormonogenesis. At 6 months of age, the mean TSH levels of all groups were still abnormally high (>7 mU/L), even though there was normalization of T₄ levels. Despite early treatment, elevated plasma TSH concentrations in the first year of life are very common in infants with CH regardless of their etiological group (13, 14, 22, 23). Accumulating data from these and other studies in which the severity of hypothyroidism was determined by parameters such as the degree of skeletal delay and T₄ and TSH concentrations suggest that the increase in TSH concentrations is related to a lower l-T₄ dose and that TSH inhibition can be attained by higher doses (11, 13, 14, 22–25). Despite having received a higher l-T₄ dose, the percentage of patients who required a dose increase in the first 6 months was significantly higher in the athyrotic group. Furthermore, in this group, TSH levels correlated inversely with l-T₄ dose at the previous visit. These findings provide strong support for the view that the etiology should be considered as an important determinant of treatment schedules in patients with CH. Accordingly, in those patients with athyrosis, more frequent follow-up visits and a higher dose of l-T₄ both at initiation of therapy and at follow-up may be required, particularly during the first 6 months of life. Other recent data also support this view (11, 16).

Our patients with athyrosis began treatment at a median age of 12 days and an initial dose of 9.4 μg/kg/day (range, 7–14). Van Vliet et al. studied 8 patients for 18 months, initiated therapy at 14 days of age, and used a median l-T₄ dose of 11.6 μg/kg/day, which was slightly higher than our dose (11). They found the developmental outcome of infants with severe CH (defined by the degree of skeletal delay and T₄ concentrations) was indistinguishable at 18 months from that of children with less severe hypothyroidism. However, some subtle differences may appear over time, especially with the use of more sophisticated neuropsychological tests (9).

Transient hyperthyroxinemia resulting from a relatively high dose regimen does not appear to produce any harmful effects (11, 12, 15, 24). Although an earlier study did report increased temperamental difficulties among infants started on a higher dose of l-T₄ (26), this dose was subsequently found to be beneficial for intellectual outcome at 7 yr of age (27). Although a high initial dose of l-T₄ therapy may be beneficial for patients with severe hypothyroidism, the advantage of this therapeutic approach over the long term remains to be proven.

It has been suggested that despite early treatment of CH, disease severity (determined mostly by T₄ concentrations and the degree of skeletal delay) has a threshold effect on prenatal brain development (7, 8). In those studies that evaluated the intellectual outcome in children with CH at 5 yr of age, the initial dose of l-T₄ ranged between 8 and 10 μg/kg (7, 8). These dose differences may explain to some degree the different conclusions reached by different investigators. In a study evaluating later neuropsychological outcome of children with CH, where the etiology was available, children with athyrosis had the lowest scores (9). These data strengthen our view that children with athyrosis need more careful evaluation and a more aggressive treatment schedule. Only long-term follow-up studies evaluating the intellectual outcome in children with CH due to different diagnostic categories will confirm whether the outcome is affected by the etiology and whether it is consistently worse in athyrosis (28). An ongoing study on a subset of our sample in whom thyroid hormone measurements and neuropsychological abilities were measured at 7–12 yr of age will provide relevant data on the clinical significance of our current findings.

An interesting finding in our study was the significant increase in TSH concentrations at 12 months in children with dysgenetic CH compared with those in the other two groups. This rise corresponds to the high proportion of patients requiring a dose increase at this time. T₄ concentrations in the dysgenetic group decreased, reaching a nadir (from 171 to 131 nmol/L) at the same time. Based on a 40% decrease in T₄ levels between screening and diagnosis, Delange et al. proposed the term vanishing thyroid tissue to explain the progressive decrease in serum T₄ in infants with thyroid dysgenesis (19). One explanation for our findings may be the loss of functional capacity of the thyroid tissue not only in the first few weeks of life but throughout the first year. In particular, the partially functioning thyroid gland of children with thyroid dysgenesis may no longer meet the metabolic needs of rapid growth by 12 months of age.

The female preponderance found in our patients with dysgenetic CH is also noteworthy. This is consistent with the observations in a recent report from Devos et al. suggesting that the molecular mechanisms resulting in athyrosis or defective thyroid migration may be “modulated by the genetic make-up of the embryo and/or the hormonal milieu of the fetus” (29).

In our patients with dyshormonogenesis, there was a prompt response to l-T₄ therapy, with serum TSH concentrations decreasing significantly by 2–4 weeks of age and remaining lowest during the first 9 months. In these patients the low TSH levels persisted throughout this time despite the fact that they received the lowest dose (micrograms per kg/day) of l-T₄, and their serum T₄ concentrations levels did not differ from those in the other two groups. In normal individuals, TSH secretion is inversely proportionate to the concentration of thyroid hormones (30). Thus, the early and marked suppression of TSH in response to therapy in the dyshormonogenetic CH group, as opposed to lack of suppression in response to a similar dose in the athyrotic group, suggests that the sensitivity of the hypothalamic-pituitary-thyroid axis to circulating T₄ may differ in the various etiological groups (15).

In children with dyshormonogenetic hypothyroidism, ongoing thyroid stimulation by normal or slightly elevated TSH concentrations may be a risk factor for the development of nodular hyperplasia later in life (31, 32). In our patients with dyshormonogenesis, slightly increased TSH levels were found later at 48 months. Thus, closer follow-up of these patients may become necessary at older ages.

The follow-up schedules in our study were similar to those employed by other groups (12, 16), but were slightly less frequent than recommended by the American Academy of Pediatrics guidelines (33). We conclude, therefore, that treat-
ment and follow-up schedules for CH need to consider the unique hormonal patterns and different responses to therapy in the three primary etiological categories. This implies that an etiological diagnosis is advisable before initiation of therapy but without delaying it, a procedure that is not routine in most centers. Although the need for close supervision in children with CH, especially those with athyreosis, is crucial, particularly during early life, those with dysgenetic and dyshormonogenetic CH may also require more attention later life.

References