0013-7227/02/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 87(7):3209–3214

Subclinical Hypothyroidism in Early Childhood: A Frequent Outcome of Transient Neonatal Hyperthyrotropinemia

FRANCESCA CALACIURA, ROSA MARIA MOTTA, GIUSEPPE MISCIO, GRAZIELLA FICHERA, DANIELA LEONARDI, ANNA CARTA, VINCENZO TRISCHITTA, VITTORIO TASSI, LIDIA SAVA, AND RICCARDO VIGNERI

Istituto di Medicina Interna, Malattie Endocrine e del Metabolismo dell'Università di Catania, Ospedale Garibaldi (F.C., R.M.M., G.F., D.L., A.C., L.S., R.V.), 95125 Catania, Italy; and Divisione ed Unità di Ricerca di Endocrinologia, Istituto Scientifico Ospedale Casa Sollievo della Sofferenza (G.M., V.T., V.T.), San Giovanni Rotondo, Foggia, Italy

Newborns with high TSH at birth and with normal free T_4 and normal or slightly elevated TSH at the confirmatory examination are considered false positive for congenital hypothyroidism. We evaluated thyroid function, thyroid antibodies, thyroid volume and morphology, thyroperoxidase and TSH receptor genes, and auxological data in 56 false positive children at 16–44 months of age. In these children thyroid function at confirmatory examination was fully normal in 33 (TSH, 0.8–4.9 mU/liter; group I) and nearly normal (borderline elevated TSH, 5.0–11.7 mU/liter) in the other 23 (group II).

Compared with 65 control children with normal TSH at birth, false positive children had significantly higher basal serum TSH (mean ± SD, 4.38 ± 2.2 *vs.* 1.4 ± 0.8 mU/liter; $P < 0.01$). Subclinical hypothyroidism, indicated by increased basal TSH and/or increased TSH response to TRH, was present in 36% children in group I and 70% in group II. Free T_4 was within the normal range in all children. Compared with the control group, false positive children had significantly higher free T_3 values (4.9 ± 0.8 *vs.* 3.7 ± 1.0 pmol/liter; $P < 0.01$) and a higher prevalence of antithyroid antibodies (25% *vs.* 1.5%; $P < 0.001$). Frequent thyroid morphology abnormalities and frequent thyroperoxidase and TSH receptor gene sequence variations were also observed.

In conclusion, newborns classified false positive at congenital hypothyroidism screening have a very high risk of subclinical hypothyroidism in infancy and early childhood. (*J Clin Endocrinol Metab* 87: 3209–3214, 2002)

CONGENITAL HYPOTHYROIDISM (CH) occurs in approximately 1 in 3000–3500 live births. If not readily treated this condition may lead to severe and irreversible mental retardation. Because signs and symptoms of CH are often scarce and not easily recognizable, newborns are screened at birth for early CH detection. TSH is measured on a blood spot obtained by heel-stick on d 3–5 of life (1–4), and all newborns with elevated TSH values (*i.e.* positive at screening) are reevaluated as soon as possible (2–4 wk of age) by both serum TSH and free T_4 (FT_4) measurements (confirmation or recall examination). Approximately 30% of all newborns with elevated neonatal TSH are confirmed CH (both elevated TSH and low FT_4 at recall examination) and are immediately started on L-T_4 treatment. Most newborns with elevated screening TSH levels (60–70%), however, have normal or nearly normal TSH and normal FT_4 at recall examination. These newborns are classified as false positive at CH screening. They are usually considered normal, especially when TSH and FT_4 values at recall examination are both normal, and no further examination is carried out. Some reports indicate that they may have persistent hyperthyrotropinemia during childhood (5–8), but the frequency and causes have not been investigated. We hypothesized that in some cases transient hyperthyrotropinemia in the newborn may be the consequence of documentable abnormalities and represent a true clinical condition with mild thyroid dysfunction that may either persist or reappear after the neonatal period.

We have carried out a prospective study in 56 false positive newborns with elevated TSH at birth, but normal serum FT_4 and normal or borderline high/normal TSH at recall examination. In these children we examined thyroid function at birth, in the neonatal period, and again at 2–3 yr of age and investigated some of the most common putative causes of CH. The study aimed to evaluate the outcome of thyroid function studies in early childhood in individuals found to be positive at CH screening and to identify the cause(s) of transient elevation of TSH at birth. A high prevalence of thyroid abnormalities and subclinical hypothyroidism was found, indicating that elevated TSH at screening, even when of very short duration, may be a clinically relevant marker of thyroid abnormalities.

Subjects and Methods

Subjects

We studied 56 children, recruited among those who, at screening examination, had a blood spot TSH higher than 20 mU/liter (40 mU/liter serum for a hematocrit of 50%). A second measurement of both TSH and FT_4 was obtained in serum on d 22.2 ± 6.2 of life (confirmation or recall examination). At this second evaluation all infants had normal serum FT_4; 33 also had fully normal serum TSH (<5.0 mU/liter; group I), whereas 23 had high normal/slightly elevated TSH (5–11.7 mU/liter; group II; Table 1) (9, 10). In the presence of a normal FT_4, the slightly

Abbreviations: CH, Congenital hypothyroidism; FT_3, free T_3; FT_4, free T_4; TPO, thyroperoxidase; TSH-R, TSH receptor.

TABLE 1. Screening and recall evaluations in 56 false positive newborns

	False positive newborns	
	Group I (n = 33)	Group II (n = 23)
Screening		
TSH (mU/liter)		
Mean ± SD	31.6 ± 11.7	32.2 ± 21.2
Range	20.1–97.0	21.3–147.5
Recall		
Age (d)	22.9 ± 7.6	25.0 ± 8.5
Range	10–47	11–49
TSH (mU/liter)		
Mean ± SD	3.0 ± 1.0	7.0 ± 1.9
Range	0.8–4.9	5.0–11.7
FT_4 (pmol/liter)		
Mean ± SD	16.7 ± 3.8	15.4 ± 2.5
Range	11.5–26.8	10.3–21.8

elevated TSH values usually are given little clinical significance, and these newborns are defined as false positive at initial screening.

Because iodine intake may influence thyroid function and TSH levels at birth (11–13), urinary iodine excretion at the recall examination was determined in 48 of 56 infants. Average urinary iodine excretion was 13.1 μg/dl (range, 4–42 μg/dl; median, 9.2). Infants with values lower than 5 μg/dl (two cases) or higher than 20 μg/dl (five cases) were evaluated again during the first 6 months of life and were found to have normal urinary iodine excretion.

Prematurity, a recognized cause of transient neonatal hypothyroxinemia (14), was present only in 1 of 56 newborns. This child, who had a gestational age of 36 wk and a birth weight less than 2500 g, was found to have abnormal thyroid function (basal TSH, 8.3 mU/liter) in early childhood (28 months), with no identified cause.

All false positive newborns with basal TSH serum values higher than 5 mU/liter (group II) were examined again during the first 3 months of life. When increased TSH (>5 mU/liter) was observed again at two separate measurements, therapy with L-T_4 was started, although serum FT_4 levels were within the normal or low/normal range (22 of 23 subjects in group II). Treatment was withdrawn 2–3 months before the present study.

We again studied thyroid function in these 56 children when they were 16–44 months old and also studied a control group of 65 children, 19–44 months of age, with normal TSH at birth and living in the same area. Auxological data were also recorded. In all cases parents gave informed consent to enter the study.

Thyroid function and morphology

TSH, FT_4, free T_3 (FT_3), and antithyroglobulin and antithyroperoxidase antibodies were measured using commercially available methods. TSH was measured by an ultrasensitive method (TSH Axsym Abbott, Rome, Italy). In our hands this assay has within-assay coefficients of variation of 6.1% and 3.7% at TSH concentrations of 0.25 and 5.5 mU/liter, respectively. Between-assay variabilities, at the same TSH concentrations, were 1.1% and 2.2%, respectively. Urinary iodine was measured by a colorimetric method. Thyroid volume and morphology were examined by ultrasound (thyroid volume reference values obtained from the literature) (15).

A TRH test (Ferring Pharmaceuticals Ltd., Kiel, Germany; 7 μg/kg body weight, iv) was carried out in 48 of 56 children by measuring serum TSH before TRH injection and 30 min later. In 8 children the test could not be carried out due to technical difficulties or parental refusal. A TSH value higher than 35 mU/liter after TRH administration was considered abnormally elevated based on data from the literature (10). No TRH test was carried out in control children for ethical reasons.

Genetic analysis of thyroperoxidase (TPO) and TSH receptor (TSH-R)

Total genomic DNA was isolated from 4-ml whole blood samples using a DNA isolation kit (Roche Molecular Biochemicals, Milan, Italy). Individual TPO and TSH-R exons were amplified using oligonucleotide primers previously described (16–18). PCRs were performed in PTC-200 DNA Engine (MJ Research, Inc., Cambridge, MA). We used two sets of primers to analyze TPO exon 8, and five overlapping amplimers to analyze TSH-R exon 10 due to their large size. PCR products were analyzed by single strand conformation polymorphism. Whenever required, PCR samples were sequenced using Sequenase version 2.0 DNA polymerase (Amersham Pharmacia Biotech, Arlington Heights, IL).

Auxological evaluation

Standing height was measured with a Harpenden stadiometer (Holtain Ltd., Crymych, Dyfed, UK). To allow the comparison between different ages and genders, height was expressed as the SD score according to the method of Tanner *et al.* (19). The SD score was obtained by calculating the ratio between measured individual height minus mean normal height value for age and gender and SD of normal mean height. Bone age was evaluated by the Tanner-Whitehouse (TW2) method (20).

Statistical analysis

Results are expressed as mean and median values; variability is indicated by SD and/or value range. Data were analyzed by *t* test and one-way ANOVA test for comparison between groups. Frequency rates were compared by χ^2 test.

Results

TSH and thyroid hormones in early childhood (16–44 months)

In early childhood basal serum TSH concentrations were significantly higher in the 56 false positive children compared with the 65 control children (4.4 ± 2.2 *vs.* 1.4 ± 0.8 mU/liter; $P < 0.01$). A significant difference was also observed when children were subdivided according to their TSH values at recall examination (control group, 1.4 ± 0.8; group I, 3.6 ± 1.6 mU/liter; group II, 5.7 ± 2.5; $P < 0.001$, by one-way ANOVA; Table 2). A serum TSH value higher than normal (>3.9 mU/liter or the 99.7th percentile of the values obtained in control children) was found in 28 of the 56 children studied (50%), 12 of 33 (36.4%) in group I and 16 of 23 (70%) in group II (Fig. 1).

Among the 48 infants who had a TRH test, 11 (11 of 31 = 33%) in group I and 10 (10 of 17 = 59%) in group II overresponded to TRH (>35 mU/liter at 30 min; Table 2).

All 56 children examined had normal serum FT_4 values, ranging from 10.2–19.3 pmol/liter (median, 15.4; mean ± SD, 14.8 ± 2.0), not different from values found in control children (15.1 ± 2.5).

In contrast to FT_4, FT_3 values were significantly higher in false positive children (4.9 ± 0.8 pmol/liter) compared with control children (3.7 ± 1.1 pmol/liter; $P < 0.01$; Table 2). A significant difference was also present between FT_3 values in groups I and II (control group, 3.7 ± 1.1; group I, 4.8 ± 0.9; group II, 5.1 ± 0.6; $P < 0.01$, by one-way ANOVA).

Thyroid antibodies

Both anti-TPO and anti-Tg antibodies were present in 7 of 56 children examined at age 16–44 months; anti-TPO antibodies were found in an additional 2 children, and anti-Tg antibodies were found in an additional 5 children (Table 2). Among the 14 children with positive antithyroid antibodies (25% of the 56 false positive children), 6 had elevated basal TSH (range, 4.6–8.2 mU/liter).

TABLE 2. Thyroid examination in early childhood

	Patients		No.	Controls (n = 65)	
1.	Basal serum TSH				
	Mean value ± SD (mU/liter)				
	Group I	3.6 ± 1.6	33		
	Group II	5.7 ± 2.5	23		
	I + II	4.4 ± 1.4	56	1.4 ± 0.8	<0.001
	Basal TSH >3.9 mU/liter				
	Group I		12/33 (36%)		
	Group II		16/23 (70%)		
	I + II		28/56 (50%)	1/65 (1.5%)	<0.0001
2.	Abnormal TRH test				
	Group I		11/31 (33%)		
	Group II		10/17 (59%)		
	I + II		21/48 (44%)		
3.	FT_4 mean value ± SD (pmol/liter)				
	I + II	14.8 ± 2.0		15.1 ± 2.5	n.s.
4.	FT_3 mean value ± SD (pmol/liter)				
	I + II	4.9 ± 0.8		3.7 ± 1.1	<0.01
5.	Antithyroid antibodies				
	AbTg + AbTPO positive		7/56 (12.5%)		
	AbTg or AbTPO positive		7/56 (12.5%)		
	Total antibody positive		14/56 (25%)	1/65 (1.5%)	<0.001
6.	Thyroid volume (ultrasound)				
	Slight enlargment		2/56		
	Slight hypoplasia		3/56		
	Hemiagenesis		6/56 (10.7%)	12/24,000 (0.05%)[a]	<0.001
7.	TPO gene				
	Sequence variations		4/45 (8.8%)		
8.	TSH-R gene				
	Sequence variations		14/45 (31%)		
9.	More than one TPO/TSH-R gene variations		3/45 (6.6%)		
10.	Auxology + bone age				
	Normal		56		

[a] Prevalence of hemiagenesis in Sicilian schoolchildren (9–13 yr).

In the 65 children of the control group only 1 child (1.4%; $P < 0.001$ in respect to the studied group) was weakly positive for anti-TPO antibodies (Table 2).

Thyroid morphology and volume

At physical examination no thyroid abnormality was detected in any of the 56 children studied. Thyroid ultrasound examination, however, indicated that 11 of 56 children (20%) had some abnormalities of thyroid morphology or volume (Table 2). More specifically, two children had diffuse thyroid enlargement (volume × 1.5): basal serum TSH at the time of examination was higher than normal in both; three children had hypoplasia of one thyroid lobe (left lobe in all cases: basal serum TSH was elevated in two of them (5.9 and 6.4 mU/liter). Six children (10.7%) had agenesis of one thyroid lobe (hemiagenesis): basal serum TSH concentrations were higher than normal in 5 of 6. In a survey carried out in 24,000 Sicilian schoolchildren, aged 9–13 yr, ultrasound examination identified 12 cases of hemiagenesis (0.05%; $P < 0.001$ *vs.* the studied group; R. Maiorana *et al.*, unpublished data). L-T_4 treatment may have affected thyroid volume in the 22 children who had withdrawn L-T_4 administration 2–3 months before examination.

Genetic analysis

The TPO gene analysis was performed in 45 of 56 children (80.3%). One mutation and 1 polymorphism were identified. Two children had a mutation in exon 16 (C→T at position 2757, causing a proline to leucine substitution in codon 906). Both children were heterozygous for the mutation that was inherited from the mother. One was also homozygous for a TSH-R polymorphism (see below). At 33 months of age her serum TSH was 4.7 mU/liter, and her FT_4 was normal (18.8 pmol/liter); she was positive for anti-Tg antibodies. The other child had normal serum values for both TSH and FT_4. Two children had a polymorphism in the intronic DNA distal to exon 16 (C→T variation 45 bases away from the splice site). Allele frequency for this polymorphism was 4.2% in the studied group *vs.* 2.6% in the control population (96 randomly selected adults). In the 2 children with this TPO gene polymorphism, basal TSH levels were 3.8 and 4.0 mU/liter; 1 of them was positive for both anti-Tg and anti-TPO antibodies.

The TSH-R gene analysis was carried out in 45 of 56 children. One mutation and two common sequence variations were detected. One child was heterozygous for a mutation in exon 10 (T→G at position 390, causing a cysteine to tryptophan substitution in codon 390) (21). At 36 months of age she had increased serum TSH (8.6 mU/liter) and normal FT_4 (16.7 pmol/liter). Ten children carried a common polymorphism in exon 1 causing a proline to threonine substitution in codon 52 (22). In the 45 false positive children studied (1 homozygous and 9 heterozygous) the allele frequency was 24.4% *vs.* 6.2% in our control population group. Seven of 10 of these children had increased serum TSH levels (range,

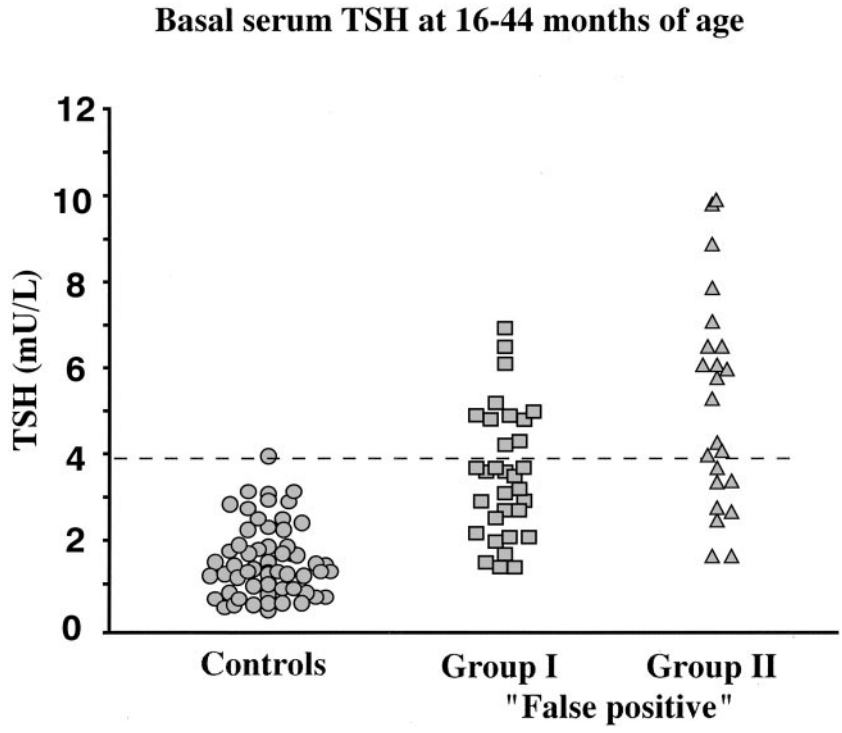

FIG. 1. A serum TSH value higher than normal (>3.9 mU/liter or the 99.7th percentile of the values obtained in control children) was found in 28 of the 56 children studied (50%), 12 of 33 (36.4%) in group I and 16 of 23 (70%) in group II.

4.6–9.3 mU/liter). Three children had a common polymorphism in exon 7 causing a phenylalanine to asparagine substitution in codon 198 (23). All of them had normal TSH levels. One child carried both TSH-R polymorphisms described above; 1 child carried both a TSH-R polymorphism and the intronic TPO gene polymorphism described above. The child homozygous for the TSH-R exon 1 polymorphism carried also a TPO mutation (see above).

Auxological parameters

Auxological data in the 56 false positive children indicated normal growth in all, as judged by the height SD score. SD scores ranged from –0.95 to +2.7. L-T_4 treatment (carried out in 22 of 56 children for an average 18 ± 6-month period; range, 10–38 months) may have affected the auxological parameters in these children, especially because the treated group had a higher percentage of subclinical hypothyroidism. The average height SD score was +0.26 ± 0.9 (range, –0.95 to +2.7) in L-T_4-treated children and +0.16 ± 0.9 (range, –0.79 to +1.79) in the untreated group. Bone age was within the normal range in all children. The ratio of bone age/chronological age was 1.09 ± 0.2 in treated children *vs.* 0.94 ± 0.2 (P = NS) in the untreated group.

Discussion

CH may be due to genetic causes such as autosomal recessive inheritance of mutations of TPO (24, 25), thyroglobulin (26), TSH-R (27, 28), and iodine transporter (29) genes. It may also be due to transcription factor mutations (30–32), which may cause thyroid dysgenesis and hypothyroidism. Environmental factors such as iodine deficiency or excess, maternal treatment with antithyroid compounds, and maternal autoimmune factors may also impair newborn thyroid function (33–35). The same factors causing CH, when less severe, may cause milder forms of hypothyroidism, including subclinical or compensated hypothyroidism. Therefore, a continuous spectrum of severity, causing various degrees of thyroid dysfunction, can occur for both genetic and/or environmental causes.

The present study identifies a group of subjects who had a short period of neonatal hyperthyrotropinemia that spontaneously remitted in the first weeks of life. However, when examined again in early childhood, some of them had mild thyroid dysfunction. The percentage of subjects with persistent TSH abnormalities in early childhood was very high (70%) among false positive children who had slightly elevated serum TSH concentrations (5–12 mU/liter) at recall examination. It was also elevated (36.4%), however, in children false positive at screening who had completely normal serum TSH (<5 mU/liter) at recall examination. Therefore, our study suggests that all infants with elevated TSH at neonatal screening are at risk for the development of subclinical hypothyroidism in early childhood (odds ratio, 44.6; 95% confidence interval, 38.8–50.4).

Very few data exist regarding the long-term outcome of newborns with transient elevated TSH at birth and normal serum thyroid hormones. Persistent hyperthyrotropinemia has occasionally been reported (5–8). In a previous study (7) the percentage of false positive children with persistent high TSH at 7–9 yr of age was lower than in our study. The cause(s) of these differences is not clear; they may be due to the different age of examination (2–3 yr in our study *vs.* 7–9 yr) and/or to different genetic or environmental factors that may differently affect thyroid function. In a more recent study (8) newborns with neonatal hyperthyrotropinemia that nearly normalized at recall examination (TSH, 5.3–18.8 mU/liter)

were treated with L-T_4 and were investigated again at 3 yr of age, as in our study. After therapy discontinuation, 13 of 14 had persistently abnormal thyroid function.

In the present study for the first time we have identified several different thyroid abnormalities in children who were false positive at screening: genetic abnormalities, thyroid gland malformations, and autoantibodies. One or more than one thyroid abnormality (genetic, immunological, and morphological) was identified in 24 of 56 children. These defects of variable severity, sometimes combined, give rise to a heterogeneous population of individuals with a moderate and sometimes intermittent TSH elevation, to compensate for the partially impaired thyroid function. This moderate thyroid insufficiency may be more evident at birth because of the less mature thyroid gland and the increased thyroid hormone requirement during neonatal life (36).

Of special interest is the high prevalence of antithyroid antibodies in children who were false positive at screening. Although in most cases the presence of antibodies was not associated with subclinical hypothyroidism at 2–3 yr of age, antibodies are a recognized risk factor for developing overt hypothyroidism (37). The high prevalence of antibodies in children who had elevated neonatal TSH concentrations, reported previously (38), makes the correlation between the two phenomena likely, although the mechanism remains unknown.

The major clinical issue raised by the present observations is the relevance of early infancy hyperthyrotropinemia in terms of consequences on the child's healthy development and thyroid function evolution. In a small series of infants with a similar TSH increase, permanent subclinical hypothyroidism and reduced basal metabolic rate were reported (39). Whether this may affect the infant's growth, health, and mental development is not known, although accumulating evidence suggests that even mild and transient hypothyroidism may be associated with adverse physical and/or neurodevelopmental consequences (40). We have observed that transient congenital hypothyroidism due to iodine deficiency may significantly impair cognitive functions. However, this occurred only when serum FT_4 levels were reduced (41), which was not the case in the present series of children.

Subclinical hypothyroidism is, by definition, asymptomatic and may be difficult to assess, requiring repeated thyroid function evaluation, because TSH values in the same individual may spontaneously fluctuate around the upper normal range, suggesting either normal or abnormal thyroid function (5, 6). It often characterizes a stage of hypothyroidism that precedes the clinical presentation of the disease, which may occur later, due either to progression of thyroid insufficiency or the occurrence of other factors such as increased thyroid hormone requirement, reduced iodine availability, thyroid gland damage by inflammation, *etc.* Longitudinal studies suggest that 20–50% of individuals with subclinical hypothyroidism develop overt hypothyroidism within 4–8 yr (42). In the Whickham survey (37), the odds ratio of developing hypothyroidism was calculated to be 8 in adult woman with either a serum TSH value higher than 6 mU/liter or positive antithyroid antibodies; the odds ratio was 38 when both conditions were present. A much higher odds ratio for developing hypothyroidism were calculated in adult men with similar abnormalities. These studies, however, were carried out in the adult population. No data are available for children.

The major concern in children with compensated hypothyroidism is that minimal end-organ abnormalities may be present, which are undetectable because of the lack of sensitive peripheral indicators such as serum TSH for the pituitary. Such minimal abnormalities may lead to important or irreversible problems over the course of many years. Lipid metabolism, myocardial function, linear growth, and cognitive ability are some of the functions that may be adversely affected by subclinical hypothyroidism (42, 43). Even mild impairment of cognitive functions may have negative consequences for the developing child, and even school achievement within the normal range does not prove that the child would not have performed better if treated with L-T_4. On the other hand, it is not an easy decision to treat infants and children on the basis of a single laboratory abnormality, even when repeatedly observed. The concerns and anxieties raised in the parents by both repeated examinations and treatment should also be taken into account. The issue, therefore, is still a matter of debate (44, 45), although the general consensus is that all subjects with a serum TSH level above 10 mU/liter and normal FT_4 will benefit from L-T_4 treatment. As far as children are concerned, further neurodevelopmental studies are required, including psychointellectual evaluation of treated *vs.* untreated children and longitudinal studies to observe the evolution of subtle thyroid function abnormalities occurring in the neonatal and early childhood periods.

After discussing the issue with the parents and paying close attention to avoid overtreatment, we decided to give L-T_4 to infants false positive at screening and with mildly elevated TSH at the recall examination to maintain both TSH and thyroid hormone levels within the normal range.

In conclusion, the present observations suggest that newborns with elevated serum TSH values at screening examination but with normal FT_4 and either normal or slightly elevated TSH at the recall examination have a high risk of subclinical hypothyroidism in infancy and early childhood. They also have an unexpectedly high prevalence of antithyroid antibodies and genetic and morphological abnormalities. These abnormalities probably make the affected children susceptible to the development of overt hypothyroidism later in life. Screening programs and recall and follow-up procedures, therefore, should take into account this risk in newborns who are false positive at CH screening.

Acknowledgments

We are grateful to Dr. L. Braverman (Boston, MA), Prof. F. Delange (Brussels, Belgium), and Dr. I. D. Goldfine (San Francisco, CA) for critical revision of the manuscript and helpful suggestions. We also acknowledge Dr. G. Parrinello and A. Mirone for their careful work in screening procedures.

Received November 7, 2001. Accepted March 22, 2002.

Address all correspondence and requests for reprints to: Prof. Riccardo Vigneri Endocrinologia, Università di Catania, Ospedale Garibaldi, 95123 Catania, Italy. E-mail address: vigneri@mbox.unict.it.

This work was supported by grants from the University of Catania (L.S., Progetti d'Ateneo, 1997 and 1998), Telethon (no. E1031), and Ministero Sanità (Ricerca Finalizzata 1997 and Ricerca Corrente 1999 to V.T.).

References

1. **Burrow GN, Dussault JH, eds.** 1980 Neonatal thyroid screening. New York: Raven Press; 1–322
2. **Fisher DA** 1991 Screening for congenital hypothyroidism. TEM 2:129–133
3. **Dussault JH** 1993 Neonatal screening for congenital hypothyroidism. Clin Lab Med 13:645–652
4. **Delange F** 1997 Neonatal screening for congenital hypothyroidism: results and perspectives. Horm Res 48:51–61
5. **Miki K, Nose O, Miyai K, Yabuuchi H, Harada T** 1989 Transient infantile hyperthyreotropinaemia. Arch Dis Child 64:1177–1182
6. **Tyfield LA, Abusrewil SSA, Jones SR, Savage DCL** 1991 Persistent hyperthyreotropinaemia since the neonatal period in clinically euthyroid children. Eur J Pediatr 150:308–309
7. **Kohler B, Schnabel D, Volger S, Gruters A** 1996 Transient hypothyroidism and hyperthyreotropinaemia: normal thyroid function and physical development at the ages of 6–14 years. J Clin Endocrinol Metab 81:1563–1567
8. **Daliva Al, Linder B, Di Martino-Nardi J, Sanger P** 2000 Three year follow up of borderline congenital hypothyroidism. J. Pediatr. 136:53–56
9. **Fisher DA** 1991 Management of congenital hypothyroidism. J Clin Endocrinology Metab 72:523–529
10. **Rapaport R, Sills I, Patel U, Oppenheimer E, Skuza K, Horlick M, Goldstein S, Dimartino J, Saenger P** 1993 Thyrotropin-releasing hormone stimulation tests in infants. J Clin Endocrinology Metab 77:889–894
11. **Sava L, Delange F, Belfiore A, Purrello F, Vigneri R** 1984 Transient impairment of thyroid function in newborn from an area of endemic goiter. J Clin Endocrinol Metab 59:90–95
12. **Oliveri A, Fazzini C, Grandolfo ME, Stazi MA, D'Archivio M, De Angelis S, Sorcini M e il Gruppo di Studio per il Registro Nazionale degli Ipotiroidei Congeniti** 1998 Ipotiroidismo congenito transitorio in aree iodocarenti. Ann Ist Super Sanità 34:331–336
13. **Delange F, Heidemann P, Bourdoux P, Larsson A, Vigneri R, Klett M, Beckers C, Stubbe P** 1986 Regional variations of iodine nutrition and thyroid function during the neonatal period in Europe. Biol Neonate 49:322–330
14. **Delange F, Dalhem A, Bourdoux P, Lagasse R, Glinoer D, Fisher DA, Walfish PG, Ermans AM** 1984 Increased risk of primary hypothyroidism in preterm infants. J Pediatr 105:462–469
15. **Ueda D** 1990 Normal volume of the thyroid gland in children. J Clin Ultrasound 18:455–462
16. **Kimura S, Hong YS, Kotani T, Ohtaki S, Kikkawa F** 1989 Structure of the human peroxidase gene: comparison and relationship to the human myeloperoxidase gene. Biochemistry 28:4481–4489
17. **De Roux N, Misrahi M, Chatelain N, Gross B, Milgrom E** 1996 Microsatellite and PCR primers for genetic studies and genomic sequences of the human TSH receptor gene. Mol Cell Endocrinol 117:253–256
18. **Frazier AL, Robbins LS, Stork PJ, Sprengel R, Segaloff DL, Cone RD** 1990 Isolation of TSH and LH/CG receptor cDNAs from human thyroid: regulation by tissue specific splicing. Mol Endocrinol 4:1264–1276
19. **Tanner JM, Whitehouse RH, Takaishi M** 1966 Standards from birth to maturity for height, weight, height velocity and weight velocity: British children 1965. Arch Dis Child 41:613–635
20. **Tanner JM, Whitehouse RH, Cameron N, Marshall WA, Healym MJR, Goldstein R** 1995 Assessment of skeletal maturity and prediction of adult height (TW2 Method). London: Academic Press; 2–108
21. **De Roux N, Misrahi M, Brauner R, Houang M, Carel J, Granier M, le Bouc Y, Ghinea N, Boumedienne A, Toublanc J, Milgrom E** 1996 Four families with loss of function mutations of the thyrotropin receptor. J Clin Endocrinology Metab 81:4229–4235
22. **Sunthornthepvarakul T, Hayashi Y, Refetoff S** 1994 Polymorphism of a variant human thyrotropin receptor (hTSHR) gene. Thyroid 4:147–149
23. **Nagayama Y, Kaufman KD, Seto P, Rapoport B** 1989 Molecular cloning, sequence and functional expression of the cDNA for human thyreotropin receptor. Biochem Biophys Res Commun 165:1184–1190
24. **Bikker H, Waelkens JJJ, Bravenboer B, De Vijlder JJM** 1996 Congenital hypothyroidism caused by a premature termination signal in exon 10 of the human thyroid peroxidase gene. J Clin Endocrinol Metab 81:2076–2079
25. **Gruters A, Kohler B, Wolf A, Soling A, deVijlder L, Krude H, Biebermann H** 1996 Screening for mutations of the human thyroid peroxidase gene in patients with congenital hypothyroidism. Exp Clin Endocrinol Diabetes 104(Suppl 4):121–123
26. **Van De Graaf SA, Cammenga M, Ponne NJ, Veenboer GJ, Gons MH, Orgiazzi J, deVijlder JJ, Ris-Stalpers C** 1999 The screening for mutations in the thyroglobulin cDNA from six patients with congenital hypothyroidism. Biochimie 81:425–432
27. **Bieberman H, Gruters A, Schoneberg T, Gudermann T** 1997 Congenital hypothyroidism caused by mutations in the thyrotropin-receptor gene. N Engl J Med 336:1390–1391
28. **Krude H, Biebermann H, Gopel W, Gruters A** 1996 The gene for the thyrotropin receptor (TSHR) as a candidate gene for congenital hypothyroidism with thyroid dysgenesis. Exp Clin Endocrinol Diabetes 104(Suppl 4):117–120
29. **Pohlenz J, Rosenthal IM, Weiss RE, Jhiang SM, Burant C, Refetoff S** 1998 Congenital hypothyroidism due to mutations in the sodium/iodide symporter. J Clin Invest 101:1028–1035
30. **Macchia PE, Lapi P, Krude H, Pirro MT, Misser C, Chiovato L, Souabni A, Baserga M, Tassi V, Pinchera A, Fenzi G, Gruters A, Busslinger M, Di Lauro R** 1998 PAX8 mutations associated with congenital hypothyroidism caused by thyroid dysgenesis. Nat Genet 19:83–86
31. **Lapi P, Macchia PE, Chiovato L, Biffali E, Moschini L, Larizza D, Bserga M, Pinchera A, Fenzi G, Di Lauro R** 1997 Mutations in the gene encoding thyroid trascription factor-1 (TTF-1) are not a frequent cause of congenital hypothyroidism (CH) with thyroid dysgenesis. Thyroid 7:383–387
32. **Clifton-Bligh RJ, Wentworth JM, Heinz P, Crisp MS, John R, Lazarus JH, Ludgate M, Chatterjee VK** 1998 Mutation of the gene encoding human TTF-2 associated with thyroid agenesis, cleft palate and choanal atresia. Nat Genet 19:399–401
33. **Delange F, Fisher DA, Malvaux P, eds.** 1985 Pediatric thyroidology. Basel: Karger
34. **LaFranchi S** 1999 Congenital hypothyroidism: etiologies, diagnosis and management. Thyroid 9:735–740
35. **Amino N, Tada H, Hidaka Y** 1996 Autoimmune thyroid disease and pregnancy. J Endocrinol Invest 19:59–70
36. **Delange F, Bourdoux P, Ketelbant-Balasse P, Van Humskerken A, Glinoer D, Ermans AM** 1983 Transient primary hypothyroidism in the newborn. In: Dussault JH, Walker P, eds. Congenital hypothyroidism. New York, Basel: Marcel Dekker; 275–301
37. **Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H, Tunbridge F, Young ET** 1995 The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf) 43:55–68
38. **Gruters A, Kohler B, Schnabel D, Helge H** 1994 Follow-up of thyroid function, thyroid size and development in children with transient neonatal hypothyroidism up to the age of 14 years. J Endocrinol Invest 17(Suppl 1):59
39. **Alemzadeh R, Friedman S, Fort P, Recker B, Lifshitz F** 1992 Is there compensated hypothyroidism in infancy? Pediatrics 90:207–211
40. **Rapaport R** 2000 Congenital hypothyroidism: expanding the spectrum. J. Pediatr 136:10–12
41. **Calaciura F, Mendorla G, Distefano M, Castorina S, Fazio T, Motta RM, Sava L, Delange F, Vigneri R** 1995 Childhood IQ measurements in infants with transient congenital hypothyroidism. Clin Endocrinol (Oxf) 43:473–477
42. **Surks MI, Ocampo E** 1996 Subclinical thyroid disease. Am J Med 100:217–223
43. **Hack AE, Pols HA, Visser IJ, Drexhage HA, Hofman A, Witterman JC** 2000 Subclinical hypothyroidism is an indipendent risk factor for atherosclerosis and myocardial infarction in elderly women: The Rotterdam Study. Ann Intern Med 132:270–278
44. **Chu JW, Crapo LM** 2001 The treatment of subclinical hypothyroidism is seldom necessary. J Clin Endocrinol Metab 86:4591–4599
45. **McDermott MT, Ridgway EC** 2001 Subclinical hypothyroidism is mild thyroid failure and should be treated. J Clin Endocrinol Metab 86:4585–4590