Factors involved in the rate of fall of thyroid stimulating hormone in treated hypothyroidism

J Raza, P C Hindmarsh, C G D Brook

Abstract

The rate of fall of serum thyroid stimulating hormone (TSH) concentrations in 32 hypothyroid infants (11 boys, 21 girls) was studied after starting treatment with thyroxine to determine whether it was influenced by initial TSH concentration or the cause of the hypothyroidism. Of 27 patients who had isotope scans before treatment was started, 11 (40%) were athyrotic, 10 (38%) had an ectopic gland, and six (22%) probably had dysmorphogenesis. Treatment was started with thyroxine at 100 µg/m²/24 hours at a mean age of 26 days (range 14-45). Serum TSH concentrations remained increased in 26 (81%) at 3 months, 20 (62.5%) at 6 months, and nine (28%) at 1 year and beyond. The mean age for serum TSH to reach the normal range was 0.79 years (range 0.15-2.1 years). Diagnosis (in 27 patients) and initial results (in 32) made no difference to the rate of fall.

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The purpose of neonatal screening for congenital hypothyroidism is to detect cases, start treatment, and achieve a euthyroid state as soon as possible. The presence of a persistently raised thyroid stimulating hormone (TSH) concentration early in treatment has been reported,¹⁻³ but the reason, its significance, and whether it matters in the face of normal circulating free serum thyroxine concentrations is unclear.

We evaluated TSH concentrations during the early phase of thyroxine replacement in children detected by neonatal screening and sought to determine whether delay in the normalisation of serum TSH concentration was influenced either by underlying diagnostic subtypes or a higher basal value.

Methods

Thirty two infants (21 girls, 11 boys) were included in the study. All tested positive on the North Thames region screening programme. A serum sample for the measurement of TSH and free thyroxine concentrations was obtained before treatment was started. On the basis of a pretreatment technetium-99m isotope scan, 27 of the patients were classified into three groups: athyrotic, ectopic, or dysmorphogenetic.

Infants were started on L-thyroxine in a standard dose of 100 µg/m²/24 hours and

followed up every two weeks for two months, twice monthly for 12 months, and three times monthly until 2 years of age.

ASSAYS

Neonatal screening was done using the IDS NeoTSH kit (Immunodiagnostic Systems Ltd, Boldon, UK). A cut off < 11 mU/l was used. The precision of the assay (coefficients of variation) was 0.8% and 6.0% at 20 and 70 mU/l respectively. Serum TSH and free thyroxine concentrations were measured using the IMX automated analyser system (Abbott Laboratories Ltd, Maidenhead, UK). The precision for the TSH assay was 5.7%, 7.0%, and 7.2% at concentrations of 0.6, 4.2, and 14.2 mU/l respectively. The precision for the free thyroxine assay was 8.4%, 4.3%, and 10.7% at concentrations of 7.6, 19.5, and 49.1 pmol/l respectively.

STATISTICS

Adequate TSH suppression was defined as a serum TSH concentration within the normal range (< 6 mU/l). Mean and standard error of mean (SEM) of initial TSH concentrations, age in decimal years, and dose of thyroxine/m² body surface area are used for presentation. One way analysis of variance was used to compare significance among groups. The statistical level of significance was set at $p < 0.05$. Pearson χ^2 was used to assess the association between a low and high normal serum thyroxine on the normalisation of TSH.

Results

Twenty seven infants had an isotope scan before starting treatment: 11 (40%) were athyrotic, 10 (38%) had an ectopic gland, and six (22%) were probably cases of dysmorphogenesis. Treatment was started at a mean age of 26 days (range 14-45) (table 1).

Serum TSH concentrations remained increased in 26 (81%) patients at 3 months, 20 (62.5%) at 6 months, and nine (28%) at 1 year and beyond. The mean age for serum TSH concentration to reach the normal range was 0.79 years (range 0.15-2.1 years). There was no difference among groups.

A normal serum free thyroxine concentration (9.3-23.8 pmol/l) was achieved within 24.6 days (range 11-77). Those infants who had an increased TSH beyond 6 months of age (n=20) had received neither a lower dose of thyroxine ($p=0.72$) nor did they have a lower mean serum free thyroxine concentration ($p=0.70$) compared with those who had early TSH suppression.

London Centre for
Paediatric
Endocrinology,
Great Ormond Street
Hospital for Children,
London WC1N 3JH
J Raza
P C Hindmarsh
C G D Brook

Correspondence to:
Professor Brook.

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Table 1 Serum TSH concentrations at diagnosis, dose of thyroxine given, and age at normalisation of TSH values in three groups of patients with congenital hypothyroidism

Classification of patients (No)	Basal TSH (mU/L)	Age for normal TSH (in decimal years)	Dose ($\mu\text{g}/\text{m}^2$)
Athyroid (11)	429.6 (89)	0.83 (0.5)	114.7 (27)
Ectopic (10)	327.5 (63)	0.73 (0.6)	97.7 (22)
Dyshormonogenesis (6)	240.4 (95)	0.79 (0.4)	101.9 (16)
One way analysis of variance (p)	0.35	0.93	0.27

Data shown as mean (SEM).

Discussion

Initial management of patients with congenital hypothyroidism requires replacement of thyroxine, which is rapidly converted to triiodothyronine, the active thyroid hormone. We consider that bypassing this process, which is designed to protect against the effects of hypertriiodothyroninaemia, is unwise, except perhaps in preterm infants.⁴ Additionally, deiodination of thyroxine in the brain may be a better way to get triiodothyronine there than via the blood.

Our findings of increased TSH at 1 year in 28% of patients agree with those of Hulse *et al* (34% at 1 year),¹ Abusrewil *et al* (38% between 5–11 months),² and Germak and Foley (23% at 1 year).⁵ The delay in the normalisation of serum TSH concentration was not influenced by the pretreatment TSH concentration nor the underlying diagnostic subtypes. This was in contrast to the findings of Germak and Foley who showed a more sensitive response to thyroid hormone replacement in infants with dyshormonogenesis.⁵

The reason for the variation in the delay of normalisation of serum TSH concentrations and whether it matters is unclear. Instances in which it is not possible to suppress TSH concentrations by increasing the dose of thyroxine are rare and the long term effects of suppressing TSH at the expense of an increase in serum thyroxine concentrations are uncertain.⁶

Possible explanations of a persistently increased TSH include undertreatment,⁷ or intermittent compliance. The dose of thyroxine we used for replacement was no different in those with a persistently increased TSH, and mean serum free thyroxine concentrations were within the normal range. We do not think that poor compliance was to blame because our data would suggest that at least 50% of individuals would be so affected. The fact that values became normal with time, and with no other intervention, also makes this explanation

unlikely. A more probable reason is that there is a variation in the maturation of the pituitary threshold for regulation of TSH release by thyroxine.⁸

It has been suggested that the use of higher doses of thyroxine to suppress increased TSH concentrations lead to an improvement in IQ at 7 years of age,⁹ but these data are not uniformly reproducible,¹⁰ and excessively high concentrations of thyroxine could interfere with neuro-psychological performance during early life. Raising the dose of thyroxine is not without hazard: behavioural difficulties and attention and arithmetic problems are associated with increased circulating thyroxine concentrations. It is commonly observed that thyrotoxic children have a poorer school performance than those with treated hypothyroidism.

Our view is that the safest course of action is to treat with 100 $\mu\text{g}/\text{m}^2/\text{day}$ of thyroxine with the intention of keeping free thyroxine concentrations within the normal range, probably towards its upper quartile, regardless of TSH concentration. This may require adjustment when controlled studies are reported comparing the effects of initial higher and lower doses of thyroxine on long term outcome.

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