Elevated TSH levels normalize or remain unchanged in the majority of children with subclinical hypothyroidism

Wasniewska M, Salerno M, Cassio A, Corrias A, Aversa T, Zirilli G, Capalbo D, Bal M, Mussa A, de Luca F. Prospective evaluation of the natural course of idiopathic subclinical hypothyroidism in childhood and adolescence. Eur J Endocrinol 2009;160:417-21.

SUMMARY

BACKGROUND Subclinical hypothyroidism (SCH) is not very common during childhood and adolescence. Although data concerning the natural evolution of this disorder in children and adolescents is very sparse, some studies find that juvenile SCH may be a benign remitting process with a very low risk for progression to overt hypothyroidism. The aim of this study was to prospectively evaluate the course of SCH in children and adolescents with no underlying diseases and no risk factors that might interfere with the progression of SCH.

METHODS This is a 2-year multicenter study that prospectively evaluated the spontaneous changes in thyrotropin (TSH) and free thyroxine (FT_4) in a pediatric population comprising patients with idiopathic SCH without other nonthyroidal diseases and with no thyroid disorders or medications affecting the thyroid gland. The study subjects were children referred by community physicians because of an incidental finding of an elevated serum TSH concentration that was discovered during an annual checkup that included TSH measurement. SCH was defined as an elevated serum TSH level of 5 to 10 μIU/ml with a normal serum FT_4 concentration of 10.3 to 24.4 pmol/L, both of which were measured twice over a 1- to 2-month interval as a requirement for admission into the study. In addition, patients were screened for thyroid immune disorders with anti–thyroid peroxidase antibodies (TPOAb) and by thyroid ultrasonography performed by the same operator at entry and at the end of the 24-month study. None of the children were taking drugs known to interfere with thyroid function or had prior head or neck radiation or a prior false positive screen for congenital hypothyroidism. The study was performed in non-iodine-deficient areas. All the children with idiopathic SCH were studied as outpatients, and after the initial evaluation, they were prospectively evaluated in the hospital at 6, 12, and 24 months. During follow-up, patients were treated with levothyroxine if they exhibited a further increase in serum TSH levels greater than 10 μIU/ml. Thyroid-function tests were determined in a fasting state and were performed in the same laboratory for each subject.

RESULTS The study subjects comprised 92 patients younger than 15 years with a mean (±SD) age of 8.1±3.0 years (range, 5.0 to 14.9). In all, 67 patients (72.8%) were prepubertal and 25 (27.2%) were pubertal. During the first 6 months of follow-up, serum TSH concentrations declined significantly (Figure 1). The mean decrement in serum TSH from baseline to the end of the study was 1.0±2.1 μIU/ml. There was no relationship between gender, age, pubertal status, and serum FT_4, which did not change during follow-up and remained in the normal range throughout the study period (Figure 1). At the end of the study, only two patients had thyroid ultrasonography revealing changes compatible with Hashimoto's thyroiditis, and the others had normal thyroid glands. Except for the two children with abnormal ultrasonography, all the patients had undetectable serum TPOAb levels.

During the study, mean serum TSH levels decreased progressively while serum FT_4 levels remained unchanged. The serum TSH returned to normal (< 5 μIU/ml) in 38 of 92 patients (41%, group A), which occurred between 6 and 12 months in 16 and between 12 and 24 months in 22 patients (Figure 2). The decrease in TSH values was similar during the earlier and later periods of decline, when the TSH declined to <2 μIU/ml in only 2 patients (5.3%) while the majority of TSH levels (68.4%) normalized to between 3 and 4.3 μIU/ml. Serum TSH did not normalize during the entire observation period in the remaining 54 patients (58.7%,

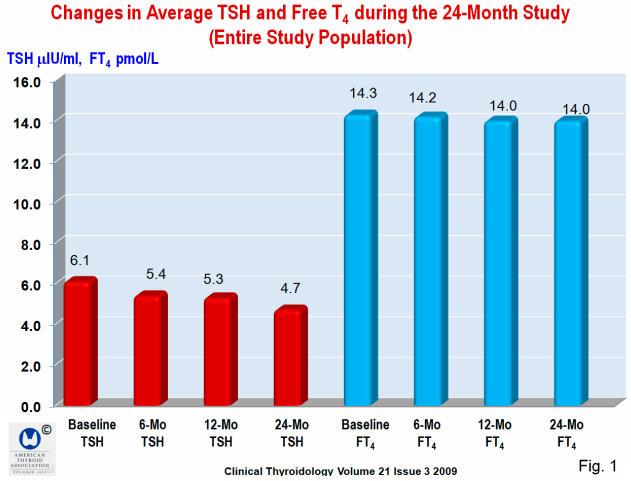

Figure 1. Changes in the average serum TSH and free thyroxine levels during the study period from baseline to 24 months, measured in the entire study population.

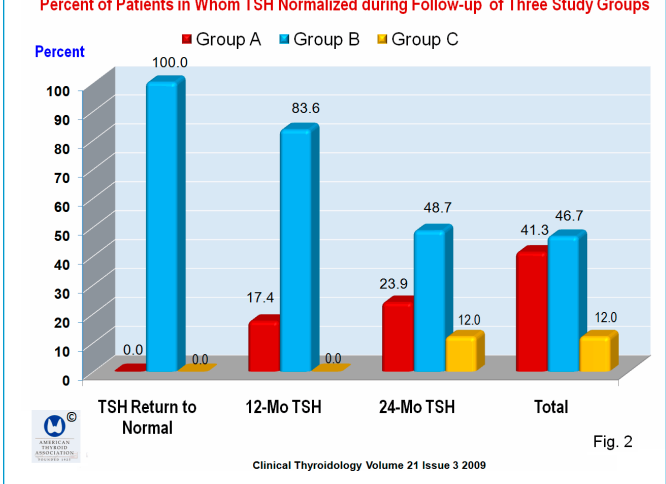

Figure 2. The changes in average TSH and free thyroxine levels in groups A, B, and C.

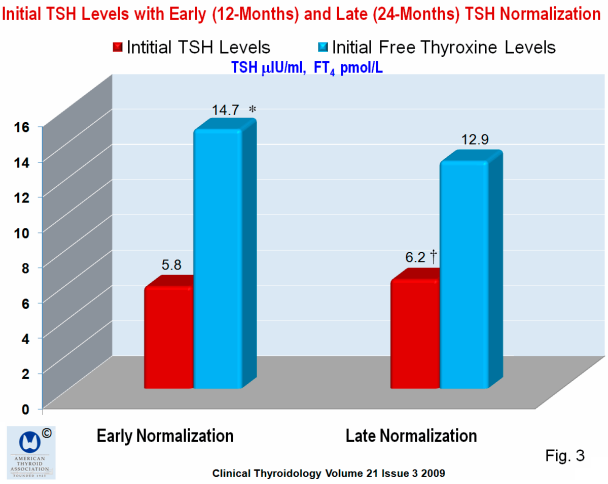

Figure 3. The initial TSH and FT_4 levels in patients who had early normalization (12 months) and late normalization (24 months) of TSH levels. *P<0.05. †P<0.012.

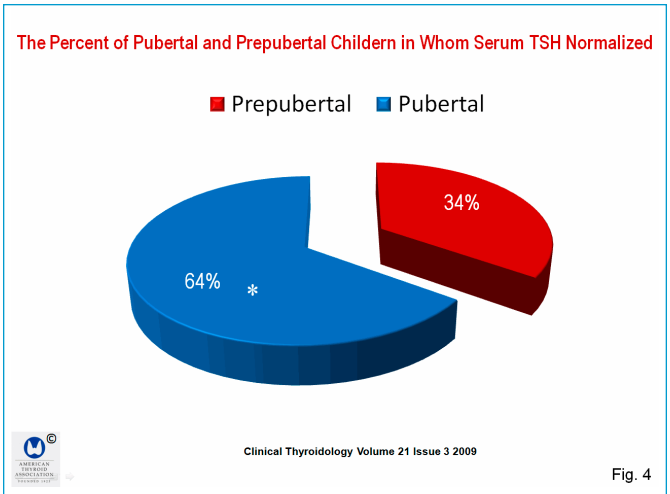

Figure 4. The percent of pubertal and prepubertal children in whom serum TSH normalized during follow-up. *P<0.05.

group B). During this time, the TSH remained between 5 and 10 μIU/ml in all but 11 patients (12%, group C) who had a further increase in serum TSH levels to between 10.5 and 15.0 μIU/ml, despite the normal FT_4 levels. In 2 of the 11 patients in group C, the TSH increase was accompanied by detectable TPOAb and ultrasonographic features of Hashimoto's thyroiditis at the end of follow-up. Initial serum TSH levels were higher among patients in whom TSH normalized late (24 months), as compared with those in whom it normalized early (12 months) (6.2±1.7 vs. 5.8±1.3 μIU/ml, P<0.0125), respectively, and the initial FT_4 levels were lower (12.9±3.3 vs. 14.7±3.3 pmol/L, P<0.05) in the two groups, respectively (Figure 3). However, even in patients in whom the TSH was slow to normalize, there was a significant decrease in serum TSH levels from baseline to 12 months (6.2±1.7 to 5.0 ±1.6 μIU/ml, P<0.05), respectively; however, there was no significant decrease in serum TSH from baseline to 12 months in the patients whose TSH did not normalize during the entire period of observation (Figure 4). The serum TSH normalized in a significantly greater number of pubertal than prepubertal patients (64.0 vs. 34.3%, P<0.01), but there were no differences between boys and girls (40.0 vs 42.8%, P>0.05).

CONCLUSION The spontaneous course of TSH levels in a pediatric population with idiopathic SCH is characterized by a progressive decrease in TSH over time in the majority of patients. This decrease was not associated with any changes in either FT_4 levels or the clinical status of the patient.

COMMENTARY

This is the first prospective study to investigate the natural evolution of SCH over time in a series of children and adolescents.

There are few studies of idiopathic SCH in pubertal and prepubertal children. Those that have been published report outcomes in patients with myriad causes of childhood SCH. For example, a study of 18 children and adolescents (age range, 5 to 19 years) with juvenile autoimmune thyroiditis with elevated serum TSH levels reported that after a mean follow-up of 5.8 years, 11 never received treatment (1). The mean duration during which the patients did not receive therapy was 47.3 months. At the end of the observation period, seven patients were euthyroid, approximately half continued to have an elevated serum TSH levels with normal serum T_4 concentrations, and only one became overtly hypothyroid. The authors suggested that juvenile SCH may be a benign process that undergoes spontaneous remission in a substantial number of patients, and that it may be possible to follow selected younger patients with a minimally elevated serum TSH concentrations rather than treating them empirically with levothyroxine. However, this is quite different from the study by Wasniewska et al., which prospectively studied only patients with no evidence of thyroid disease, including Hashimoto's thyroiditis, at the time of enrollment and autoimmune thyroiditis developed in only 2 patients after 24 months of observation. Another study of newborns with high TSH levels at birth and with normal FT_4 and normal or only slightly elevated TSH, which is considered to be false positive congenital hypothyroidism, concluded that newborns classified as false positive for congenital hypothyroidism have a very high risk of SCH in infancy and early childhood (2), an observations confirmed by other studies (2).

The study by Wasniewska et al. is unique. The patients were carefully screened for other causes of SCH, including false negative congenital hypothyroidism. The patients underwent a follow-up of 2 years without therapy except for two patients in whom hypothyroidism developed. None of the patients in this study had any clinical signs or symptoms of hypothyroidism during their entire follow-up. Moreover, none of the patients showed any symptoms of hypothyroidism during follow-up, and there were no significant changes in both height and body-mass index throughout the observation period, although group C children were

overweight and remained so from the time of entry to the close of the study. By the end of the study, the percent of individuals who were overweight was slightly higher in group C but this was not statistically significant. The authors of this study concluded that the natural course of TSH elevations in a pediatric population with SCH is characterized by a progressive decrease over time and that the majority of patients have a normalization of, or stable mild increase in serum TSH with normal serum FT_4 concentrations. The data in this study are robust, which along with other studies (3-5) provide much proof for the authors' conclusion that TSH determination has no reason to be part of the routine checkup in children, except for specific protocols.

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