Autonomously functioning thyroid nodule

A study of 67 patients from an iodine-deficient area

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■ Sixty-seven patients with autonomously functioning thyroid nodule (AFTN) had either euthyroid or toxic nodules, according to clinical, biochemical, and dynamic studies. The subjects were residents of regions of Iran known to be iodine deficient. The prevalence of hyperthyroidism and T3 toxicosis was greater than in iodine-sufficient areas, and AFTN and toxic nodules occurred at a younger age range (74.6% of subjects were age 20–49 years) than in iodine-sufficient areas. One-fourth of the subjects had hyperthyroidism and 35.5% of the hyperthyroid patients had T3 toxicosis. The sex distribution showed a lower female-to-male ratio in patients with AFTN (3.7:1) and in patients with toxic nodules (1.8:1) than earlier studies showed. There was some discrepancy in the results of T3 suppression and TRH tests; nine subjects with nonsuppressible nodules (T3 suppression) had normal TRH responses. Forty (81.6%) patients with euthyroid AFTN had no response to TRH stimulation. There was a good correlation between I-131 and Tc-99m scans.

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AN AUTONOMOUSLY functioning thyroid nodule (AFTN) is a discrete nodular structure. Unrelated to extranodular tissue, its function, growth, and iodine uptake are independent of thyroid-stimulating-hormone (TSH) action.[1] These nodules concentrate radioactive iodine more actively than extranodular tissue and can be identified on thyroid scans.[2] The exogenous administration of tri-iodothyronine or thyroxin does not suppress the activity of these nodules because their function is independent of TSH.[3] Although AFTNs have been reported in the United States,[4] more cases have been reported in Europe and South America.[5–7]

The purpose of this study is to evaluate the clinical and functional characteristics of AFTNs in patients from an iodine-deficient area where goiter is prevalent.[8] We were specifically interested in answering the following questions:

1. What percentage of patients with an AFTN and from a specific iodine-deficient area are hyperthyroid?
2. Are the age and sex distributions different from those living in iodine-sufficient areas?
3. Does the rate of hyperthyroidism increase with age?
4. What is the status of TRH (thyrotropin-releasing-hormone) responsiveness in the euthyroid patients with AFTN?
5. What is the correlation between TRH stimulation test and T3 suppression test results in euthyroid AFTN?
6. Do thyroid scans using Tc-99m and I-131 show some correlation regarding the functional activity of the nodules?

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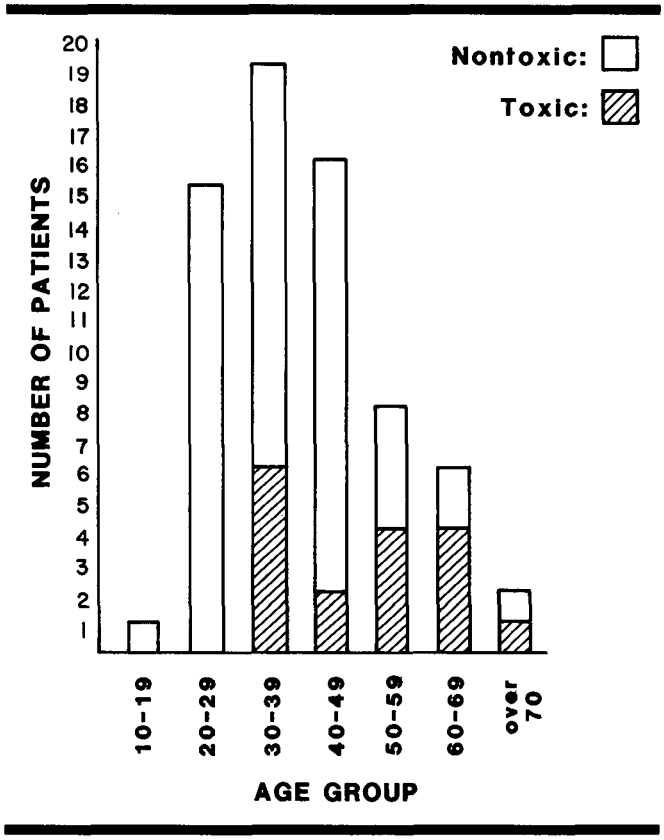

Figure. Age distribution for toxic and nontoxic nodules.

TABLE
SEX DISTRIBUTION OF 67 PATIENTS IN RELATION TO THYROID FUNCTION

No. patients	Female	Male
Nontoxic nodule	42 (62.6%)	8 (12%)
Toxic nodule	11 (16.4%)	6 (9%)

MATERIALS AND METHODS

We studied 67 patients who presented with a discrete "hot" thyroid nodule, as shown on scans obtained between September 1984 and March 1986. The extranodular tissue was completely suppressed in these patients. Fifty (74%) of the patients were from the Tehran area and the localities at the foot of the Alborz Mountains; the remainder were from other areas of Iran known to be iodine deficient. The average diameter of the nodules was 3.6 cm in euthyroid patients and 4.5 cm in hyperthyroid patients. Most patients were referred to us by local physicians. All patients underwent careful clinical examination. Total serum T3 and T4 values were measured. T3 radioactive iodine uptake (RAIU) was determined after two and 24 hours. Tc-99m thyroid scans (rectilinear scanner) were obtained for all patients. Normal values were: T4 = 4.5–12 μg/dL, T3 = 80–200 ng/dL, T3 RU = 25%–37%, and TSH = 0.3–4.5 μU/mL. The I-131 thyroid scan was also obtained for 50 patients. Depending on the results of these investigations, patients were classified as euthyroid or hyperthyroid.

Euthyroid patients

A TRH stimulation test was performed for 49 of 50 patients. TRH (Portirelin, 400 μg) was injected intravenously and serum TSH was measured at 0, 30, and 60 minutes. Next, a T3 suppression test using tri-iodothyronine (Liothyronine sodium) (25 μg tablet, three times daily) was performed for 32 of the 49 patients. RAIU was measured two and 24 hours before and nine and 10 days after T3 suppression. We considered a 5–30-μU/mL increment of serum TSH at 30 minutes[9,10] and 50% reduction of 24-hour RAIU[11] as indicative of normal response. Autonomy was defined as nonsuppressible RAIU plus either a positive I-131 thyroid image following T3 suppression or a TRH stimulation test showing no response.[12]

Hyperthyroid patients

The thyroid-function test was used to detect hyperthyroidism; TRH stimulation and T3 suppression tests were not performed. In addition to clinical findings, the criteria for diagnosing hyperthyroidism included a serum T4 level of more than 12 μg/dL and/or a serum T3 measurement of greater than 200 ng/dL. Alterations in binding capacity were determined based on the T3 RU. Patients with elevated T4 or T3 values because of increased thyroxin-binding globulin were not included in this group. In three patients with mild T3 toxicosis, the TRH stimulation test was used to confirm the presence of hyperthyroidism.

RESULTS

The mean serum T4 value was 8 ± 1.7 μg/dL (mean ± SD) and serum T3 was 145.5 ± 29 ng/dL in euthyroid patients. In the hyperthyroid group, mean serum T4 was 14 ± 2.9 μg/dL and T3, 270 ± 63 ng/dL.

Clinical and biochemical hyperfunction was diag-

nosed in 17 of 67 patients (25.3%). Six patients had T3 toxicosis (35.3% of the hyperthyroid group) with a mean serum T4 value of 10.6 ± 0.7 μg/dL and T3 measurement of 230 ± 21 ng/dL. The TRH test was performed in three of these patients and showed no response.

The age distribution of patients with toxic and nontoxic nodules is shown in the *Figure*. Fifty patients (74.6%) were between 20 and 49 years old; only eight of these patients (12%) had hyperthyroidism. Sixteen patients (24%) were over the age of 50 and nine of these (56.2%) had hyperthyroidism. We found no evidence of hyperthyroidism in 16 patients (23.8%) below the age of 29. The female to male ratio for all patients with AFTN was 3.7:1. Sex distribution is shown in the *Table*.

The TRH test was performed for 49 euthyroid patients; in 40 instances (81.6%), no response was shown. Nine patients (18.3%) responded normally. The serum T4 and T3 levels in these patients with normal TRH response were 7.6 ± 2 μg/dL and 120 ± 20 ng/dL, respectively.

We performed the T3 suppression test after the TRH test for 32 of 49 euthyroid patients. All of these patients had nonsuppressible RAIU, and nine of them had normal TRH responses. Mean TSH increments of 12.7 ± 8 μU/mL were observed after 30 minutes in these patients.

In euthyroid patients, the mean two-hour RAIU was 21%; the 24-hour RAIU was 26% before the T3 suppression test and 47% after the test. In the hyperthyroid group, the mean two-hour RAIU was 34.7% and the 24-hour measurement was 65.8%. The normal value for RAIU is considered to be 10%–20% at two hours and 40%–50% at 24 hours.

In 50 patients considered clinically and biologically euthyroid, both I-131 and Tc-99m scans were available and correlated with each other, except for one case in which the size of the nodule was greater on the Tc-99m image. Thyroid scans also were obtained after T3 suppression in 32 of these patients and showed no remarkable changes in the surface area of the nodules.

DISCUSSION

Concepts regarding diagnosis, clinical features, and pathogenesis of functioning thyroid nodules have been evolving since the first description of toxic adenomatous goiter by Plummer.[13] The functioning nodule is caused by adenomatous hyperplasia, benign adenoma, or localized nontoxic nodular goiter.[14] Either compensatory hyperplasia secondary to contralateral impairment in function or the rare asymmetric goiter of Graves' disease may simulate functioning adenomas.[1,15] The clinician is usually confronted with a palpable nodule and a solitary "hot" area on the scan.

We tried to study the functional and clinical characteristics of these nodules in patients from an iodine-deficient area. An analysis of drinking water[8] has shown that goiter, as it occurs in Iran, is most likely due to lack of an adequate supply of iodine. There has been no attempt to correct the iodine deficiency. Patients were classified into either "euthyroid-autonomous" or "toxic-nodule" groups based on clinical judgment, biochemical data, and the results of dynamic studies.

The incidence of AFTNs differs in various parts of the world, being greater in iodine-deficient areas.[7] The percentage of toxic functioning nodules and also T3 toxicosis is higher in areas where goiter is endemic.[7] Nearly one-fourth of our patients had hyperfunctioning nodules and 35.3% of those had T3 toxicosis. The mean serum T3 level of this group was lower than that of patients who had both elevated serum T4 and T3 levels. This may indicate that T3 toxicosis is an early stage of hyperthyroidism.

AFTN is more common among older age groups in iodine-sufficient areas,[16] but 74.6% of our patients were between 20 and 49 years old. The incidence of hyperthyroidism in our study was 25%; Hamburger[1] reported an incidence of 14.6%, but Belfiore et al[7] reported a higher percentage in an iodine-deficient area. Of our 50 patients (74.6%) below age 49, eight (16%) had hyperthyroidism; Hamburger[1] reported 64% of patients under age 49, 3.6% of whom had hyperthyroidism. These data all show that both AFTN and hyperthyroidism appeared at a younger age in our subjects than in persons who live in iodine-sufficient areas.

The sex distribution of these 67 AFTN patients is of special interest. We found a female-to-male ratio of 3.7:1, in comparison to 10:1 reported by Hamburger[1] and 11.2:1 reported by Belfiore et al.[7]

By which criteria should the autonomy of these nodules be defined?

Nine of our patients with nonsuppressible nodular activity, as shown by the T3 suppression test and the I-131 scan, had normal TRH response, indicating a discrepancy between TRH-stimulation and T3-suppression tests in some patients. This may be explained by the existence of an autonomously functioning area of the thyroid that nevertheless does not overproduce thyroid hormone.[17] Considering this, the TRH test seems to be more sensitive for demonstrating the functional capacity of the AFTN. Also, patients with a normal TRH response have functioning normal thyroid tissue, whereas

patients with no TRH response have little or no normal thyroid tissue, as visualized on scans. We found a significantly high number of patients with euthyroid AFTN and no response to TRH stimulation; in time, toxicosis may develop in these patients.

Although Usher and Arzoumanian[18] reported inconsistencies between the two scans, we found that I-131 and Tc-99m images correlated well. The RAIU was noticeably high in both of our patient groups, and higher levels were evident when hyperthyroidism was present. Consequently, it is possible that in iodine-deficient areas ablation of these nodules with I-131 may be achieved by lower dosages.

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