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Retrospective Evaluation of Thyrotoxicosis: Cerrahpaşa Experience

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The aim of this retrospective study is to assess the annual incidence of different types of hyperthyroidism (HT) and to report our experience with antithyroid therapy in Graves' disease after iodized salt prophylaxis in Turkey from 1990 to 2000. For this purpose the outpatient files of 12574 thyroid patients were revised. Clinical examination, serum TSH, thyroid hormone levels, serum thyroid autoantibody titers, thyroid ultrasonography and scintigraphy were defined before diagnosis. HT was classified as immunogenic HT [Graves' disease, (GD)] and HT with intrinsic thyroid autonomy [Toxic Multinodular Goitre (TMG) and Toxic Adenoma (TA)]. Hyperthyroidism was determined in 766 (6.09%) out of 12574 thyroid patients. The diagnoses were as follows: GD 54.5%, TMG 39.6%, TA 4.6% and Subacute Thyroiditis (ST) 1.04%. The time course of different types of HT was different: after the use of iodine in the 1990's the annual distribution of HT per year was decreased in TMG (p=0.001, r=-0.846) and increased in GD (p=0.001, r=0.916). The mean observation period was 42.3±10.6 months in the patients with GD. Increased TSH Receptor Antibody (TSHRAb) titers were measured in only 55.6 % of all the patients with GD. The annual distribution of increased TSHRAb ranges per year did not change, but the mean TSHRAb level was increased. The mean TSHRAb titer was doubled in 2000 compared to 1990. Treatment with antithyroid drugs (ATD) was the first choice in GD (94.7%). The mean course of ATD therapy was 18±5.7 months and the induction interval of remission was 2±1.4 months. In 3 years follow-up 87.2% of patients were still in remission, whereas 13.8% had relapsed once and 0.47% had relapsed twice. The probability of relapse correlates weakly with TSHRAb level (p=0.04, r=0.295), length of remission (p=0.031, r=0.264) and is negatively correlated with time to induction remission (p=0.002, r=-0.379). The course of ATD therapy was correlated neither with relapse frequency (p=0.606, r=-0.082) nor with duration of remission (p=0.796, r=0.026).

Our data indicated that the frequency of GD and the detectable TSHRAb levels were increased with iodine prophylaxis. We suggest that antithyroid drugs have a significant role in the first stage treatment of GD, especially in a population with low THSRAb levels. The treatment with ATD could be more successful if the dose is reduced at the exact true point of time that is determined according to the clinical and laboratory remission criteria.

Key words: Thyrotoxicosis, Graves' disease, iodine replacement therapy

Introduction

Iodine deficiency has been reported to facilitate the development of toxic nodular goitre, whereas iodine supplementation in iodine deficient areas may increase the prevalence of autoimmune thyroid disorders. Graves' disease (GD) is caused by circulating autoantibody against thyrotropin receptor (TSHRAb) (1). Although almost all cases

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of hyperthyroidism (HT) in Graves' disease (GD) can be controlled with antithyroid drugs (ATD), the rate of permanent remission is disappointing. Besides several clinical factors, lower remission rates in GD may be related to the dietary iodine content of the country (2). Earlier reports from Turkey have established the region to be an area of endemic iodine deficiency with prevalence of goitre recorded as 30.5% (3,4). Urinary iodine excretion levels were usually measured lower than 50 µg/L. However salt iodization has been started first in 1990 and iodized salt prophylaxis in 1999 formally. The aim of this prophylaxis was to raise urinary iodine excretion more than 100 µg/L and iodine content of the salt more than 50–70 mg/ kg. ATD therapy is still the first choice of HT in GD in our country. We report a retrospective study with antithyroid therapy of GD and annual incidence of different types of HT after iodized salt prophylaxis from 1990 to 2000 in Turkey, which has endemic iodine deficient areas.

Materials and Methods

The outpatient files of all hyperthyroid patients seen in our thyroid clinic between 1990-2000 were classified according to their etiologies. The diagnosis and the type of HT were defined according to clinical examination, serum TSH and thyroid hormone levels, serum thyroid autoantibody titers and thyroid ultrasonography and scintigraphy. Hyperthyroidism was classified into immunogenic HT [Graves' disease, (GD)] and HT with intrinsic thyroid autonomy [Toxic Multinodular Goitre (TMG) and Toxic Adenoma (TA)].

The outpatient files of all patients with an established diagnosis of GD were reviewed retrospectively. Hyperthyroidism due to GD was diagnosed according to clinical signs and symptoms, suppressed serum TSH concentration, elevated serum thyroxine (T_4) and triiodothyronine (T_3) concentrations, and increased uptake of radioactive iodine by the thyroid gland. Nodular goitre was excluded by palpation or ultrasonographic examination of the thyroid.

Patients' age, sex, geographical origin, observation period, the method of therapies, remission rate, course of antithyroid drug therapy, induction interval and duration of remission, constant remission rate, relapse rate and the factors that correlate with relapse were also determined.

The following definitions of terms guiding data collection were used. Remission was defined as an absence of signs and symptoms of thyrotoxicosis and normal thyroid function studies for a period of minimum 6 months after antithyroid drugs were stopped. Relapse was defined as a recurrence of symptoms and biochemical abnormalities consistent with thyrotoxicosis after remission had occurred.

Plasma triiodothyronine (T_3) (normal values: 87-178 ng/dL), thyroxine (T_4) (n.v.: 6.09-12.23 µg / dL) and thyrotropin (TSH) levels (n.v.: 0.15-3.7 IU/ mL) were assayed by immunoassay (Beckman Coulter, Maine, USA) whereas thyroglobuline antibody (Anti TG) (n.v. <100 IU/mL) and thyroid peroxidase antibody (Anti TPO) (n.v. <100 IU/mL) levels were determined by enzyme chemiluminescent immunometric assay (DPC, LA, USA) during the diagnosis. TSH receptor antibody (TSHRAb) levels were measured by radioreceptor assay (Immunotech, Maine, USA, n.v.: 8-14 ng/dL) (5).

Practiced therapies of HT were ATD (propylthiouracil, methimazole), radioiodine treatment (RAI) and surgery. Propylthiouracil was the most commonly used thionamide in the groups.

Results were expressed as the mean ± SD. The Pearson product-moment correlation coefficient was used to evaluate the degree of correlation between all parameters. A value of $p<0.05$ was considered statistically significant. Calculations were made using SPSS software (SPSS, Inc. Evanston, IC).

Results

Hyperthyroidism was determined in 766 (6.09%) out of 12574 thyroid patients in a 10-year interval. The sex, age, thyroid hormone levels at the diagnosis and the distribution of residency in endemic goitre regions of the patients were shown in Table 1.

The etiology of HT was GD in 54.5%, TMG in 39.6%, TA in 4.6% and ST in 1.04% of patients. The annual distribution of each disease per year was also revised. The annual distribution of HT per year was decreased for TMG ($p=0.001$, $r=-0.846$) and increased for GD between 1990 and 2000 years ($p=0.001$, $r=0.916$) (Figure 1).

As Hatemi et al. reported previously, 49.6% of 766 hyperthyroid patients (52.8% of BG, 81.8% of

Table 1. The sex, age, thyroid hormone levels at the diagnosis and distribution of residency in endemic goitre regions of the patients.

	Graves' Disease	Toxic Multinodular Goitre	Toxic Adenoma	Subacute Thyroiditis
Percentage (%	54.5	39.6	4.6	1.04
Sex (Male / Female) (%)	39.6 / 81.1	21.8 / 78.2	30.7 / 69.3	25 / 75
Age (Mean ± SD years)	34.7 ± 13.14	48.8 ± 15.49	50.75 ± 10.72	39.37 ± 7.22
Endemic goitre region (%)	52.8	81.8	65.7	12.5
TT_3 (ng / dL)	325.85 ± 156.85	268.54 ± 140.38	234.42 ± 95.3	204.96 ± 42.22
TT_4 (µg / dL)	16.55 ± 7.96	14.71 ± 7	13.02 ± 4.79	12.15 ± 3.46
TSH (IU / mL)	0.078 ± 0.11	0.091 ± 0.09	0.085 ± 0.09	0.039 ± 0.051

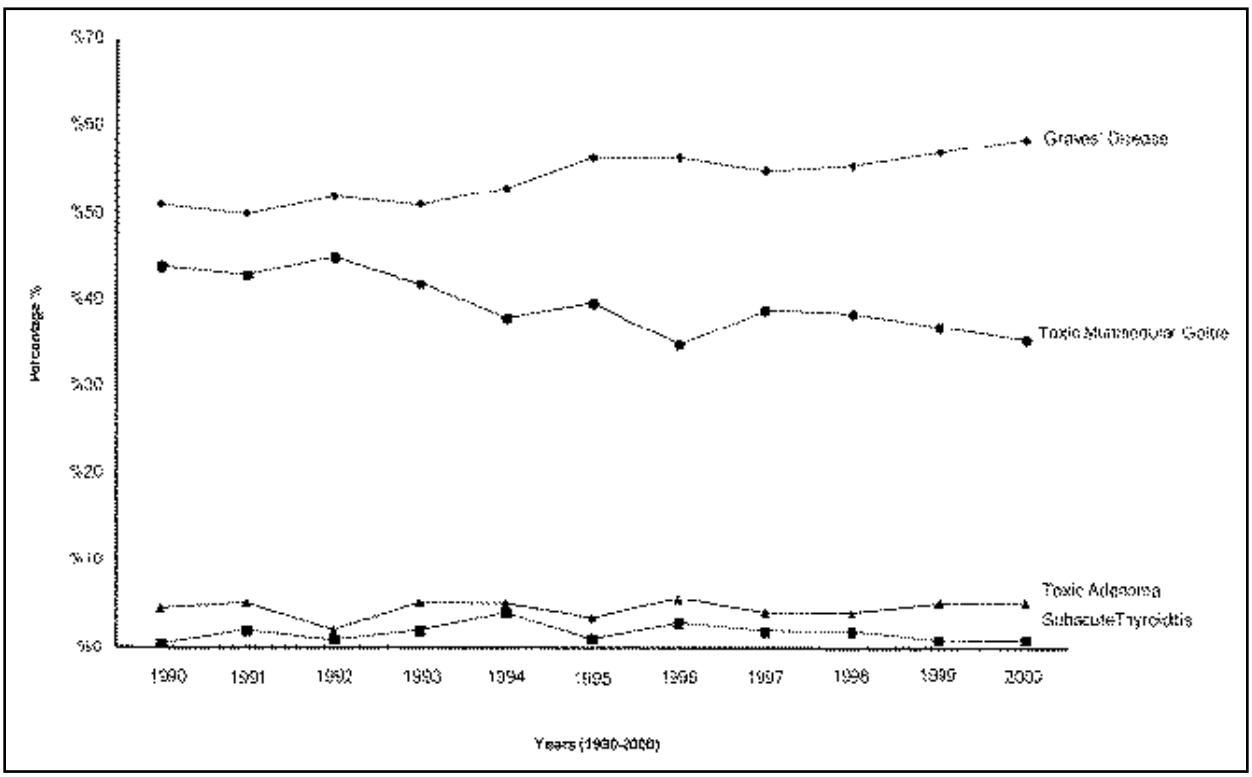

Figure 1. Changes in etiologic causes of hyperthyroidism in the period of ten years.

TMG, 65.7% of TA and 12.5% of ST) were living in endemic regions (3,4).

Detectable TSHRAb levels with thyroid stimulating activity were determined in 55.6% of untreated hyperthyroid patients with GD. The percentages of detectable thyroid autoantibodies in Graves' patients were shown in Table 2. Although, we observed an increase in mean TSHRAb levels with iodine prophylaxis, there was no change in the percentage of TSHRAb positivity (Figure 2 and Table 2). Mean TSHRAb titers were doubled in 2000 (32.7 ± 6.32 SD ng/dL) compared to 1990 (14.5 ± 5.27 SD ng/dL).

The mean observation period was 42.3 ± 10.6 months in the patients with GD. In our Graves' population 94.7% of all patients were treated with ATD, 3.9% with RAI and 1.5% with thyroid surgery. The mean course of ATD therapy was 18 ± 5.7 months and the induction interval of remission was 2 ± 1.4 months.

The remission rate was 87.2% and 13.8% of all patients were relapsed once in 3 years follow up, whereas the mean duration time of the remission was 18 ± 5.2 months in the relapsing group. The first relapse developed within 8.9 ± 10 months after stopping the therapy. In the relapsed patients the preferred therapy was ATD again, and the remission rate in this group was 96.6%. A second relapse was seen only in 3.4% of this group.

TMG patients were treated with RAI (87.2%) and thyroid surgery (12.8%).

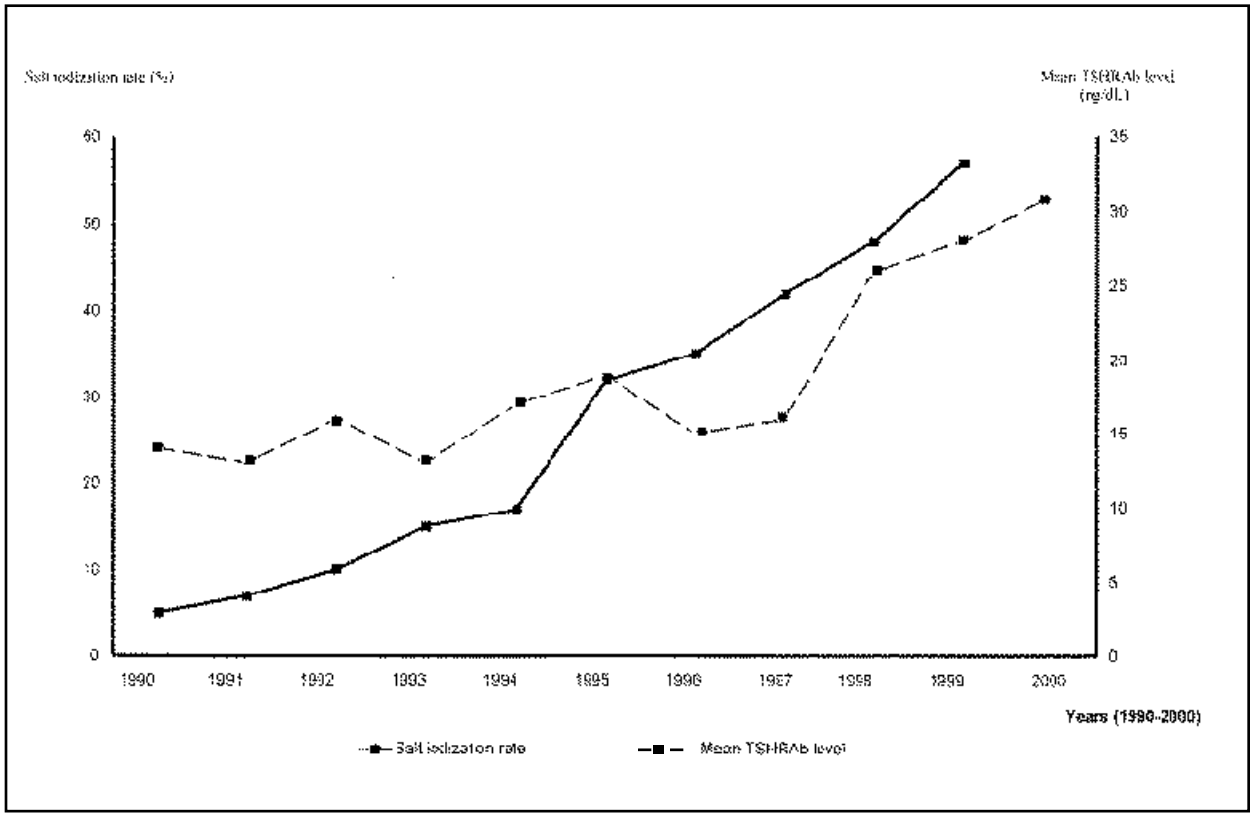

Figure 2. Relationship between salt iodinisation rate and the mean TSHRAb levels in Turkey per year.

Table 2. Comparison of the annual distributions of increased TSHRAb ranges and mean TSHRAb levels.

Years	Increased TSHRAb ranges (%)	TSHRAb levels (Mean ± SD ng /dL)
1990	58.8	14.5 ± 5.27
1991	53.2	13 ± 3.18
1992	55.3	16.9 ± 3.66
1993	61	13.7 ± 4.27
1994	53.4	17.2 ± 5.2
1995	55.5	19.36 ± 3.87
1996	49.7	15.62 ± 4.39
1997	53.5	16.85 ± 2.56
1998	57.8	26.5 ± 5.93
1999	54.3	28.5 ± 6.65
2000	59.8	32.7 ± 6.32

The relapse frequency correlated weakly with TSHRAb levels (p=0.04, r=0.295), the induction interval of remission (p=0.002, r=-0.379), and the duration of remission (p=0.031, r=0.264). The course of ATD therapy was correlated neither with relapse frequency (p=0.606, r=-0.082) nor with duration of remission (p=0.796, r=0.026).

Discussion

This study indicates that, the causes of hyperthyroidism and the clinical characteristics of Graves' disease were changed by iodine prophylaxis in Turkey. After the ISP had been started in the 1990's the proportional distribution of TMG per year decreased. On the other hand there was an increase in GD. It was published that autoimmune thyroid disease, thyroid autoantibodies and histopathological lymphocytic infiltration of the thyroid were much more common in iodine-sufficient areas (ISA) than in iodine-deficient areas (IDA) (6). Baltisberger et al. reported that the incidence of TMG in IDA decreased after full correction of mild iodine deficiency, whereas a change from IDA to ISA had been causing a permanent increase in overt and subclinical GD including increased TSHRAb levels (7).

It was written that detectable TSHRAb levels existed in 80% of patients with GD (8). In our study, the detectable TSHRAb ranges were lower (55.6%) compared to the literature, but there was an increase in the mean TSHRAb level per year, which was probably due to iodine replacement. (Figure.2).

ATD were used in 94.7% of Graves' patients and relapse was seen in only 13.7% of them. After the second ATD treatment, relapse occurred in only 3.4% of these patients. This high remission rate might have been determined because of the relatively short observation period (42.3 ± 10.6 months) in our outpatient clinic; so late relapses could not have been noticed. In fact, a high relapse range of hyperthyroidism in GD, which amounts up to 79%, was published after a ten-year follow-up after antithyroid treatment (9). ATD were preferred to RAI because of its high remission rate and minimal side effects. Recently, treatment with ATD has become the initial option in some European countries for the treatment of hyperthyroidism due to GD.

There are several factors likely to influence the course of GD after stopping the antithyroid drugs. We determined these factors as TSHRAb levels and induction interval of remission. It was also previously written that increased TSHRAb levels raised the relapsing frequency in GD (10). Studies in areas of dietary iodine sufficiency suggested that measurement of the antibodies at various stages in the course of GD might be of value in predicting the outcome of therapy (11). However, in areas of iodine deficiency, difficulties in the ability of patients' thyroid tissue to recover from the effects of antithyroid drugs may prevent the receptor antibodies from causing a relapse of thyrotoxicosis. On the other hand it was reported that the predictive value of receptor antibody measurements would be expected to be lower in iodine deficient areas (11). Our results showed that TSHRAb levels could be used as a predictive factor in GD remission, even in iodine deficient areas. The importance of the course of the therapy with ATD in GD for permanent remission was not clearly determined in the literature. It has been accepted that one to two years of control of GD is probably required to have a permanent remission after drug withdrawal, but Greer et al (12) showed that remission rate was also good when ATD were used less than six months. The mean course of ATD therapy in our study was 18 ± 5.7 months. We also could not show any correlation between the course of ATD and remission rate in our Graves' population. On the other hand the negative correlation between relapse frequency and induction interval of remission showed that there was a high relapsing frequency in the patients with early remission. The reason for this was probably reducing the dose of ATD earlier and getting less benefit from immuno-suppressive effects of these drugs in terms of time and effectiveness. Immunosuppressive effects of these drugs were published and they are probably effective in the remission of GD (13-15).

According to the literature, the frequency of long term remission occurring after withdrawal of antithyroid treatment has decreased over the past 30 years (16,17), in part because of the increase in dietary iodine intake but also the constant and low intake of iodine seen in geographic regions. Nevertheless about one third of patients experience a lasting remission.

In conclusion, these data indicated that antithyroid drugs have a significant role as sole therapy in the first stage treatment of GD, especially in a population with low THSRAb levels, living in iodine deficiency areas. Our results also showed that treatment with ATD could be more successful if the dose is reduced at the exact true point of time that is determined according to the clinical and laboratory remission criteria.

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