Graves' disease is the most common cause of severe hyperthyroidism that is accompanied by greater than usual clinical signs and symptoms and laboratory abnormalities

Iglesias P, Dévora O, García J, Tajada P, García-Arévalo C, Díez JJ. Severe hyperthyroidism: aetiology, clinical features and treatment outcome. Clin Endocrinol (Oxf) 2009; August 4 [e-pub ahead of print].

SUMMARY

BACKGROUND Graves' disease occurs in approximately 0.5% of the population and is the cause of 50 to 80% of the cases of hyperthyroidism. Although the disease generally responds to therapy, severe hyperthyroidism is a serious problem that may pose a threat of survival and thus requires a high level of therapeutic expertise and experience. The aims of this study were to analyze the clinical and laboratory features and outcomes of patients with severe hyperthyroidism and to compare these findings with the features of less-threatening forms of hyperthyroidism.

METHODS This is a retrospective observational cross-sectional study of patients with severe hyperthyroidism who attended the authors' clinic in the Department of Endocrinology, Hospital Ramón y Cajal, in Madrid, Spain, which is in the central area of Spain, a geographic area of low to sufficient iodine intake. The study subjects were patients who attended the clinic for a period of 6 months from January 1, 2006, through June 31, 2006. Excluded from the study were patients with clinical evidence of thyroid storm, subclinical hyperthyroidism defined as a suppressed serum thyrotropin (TSH) with normal free thyroxine (FT_4) and free triiodothyronine (FT_3) levels. Patients were randomly assigned to one of three groups according to the severity of hyperthyroidism as mild (mH), moderate (MH), and severe (SH) based on serum FT_4 levels: SH = FT_4 >7.8 ng/dl (normal range, 0.85 to 1.8) [>100 pmol/L {normal range, 11 to 23}]; mH = FT_4 1.8 to 3.9 ng/dl [23 to 50 pmol/L], and MH = FT_4 3.9 to 7.7 ng/ml [50 to 99 pmol/L].

RESULTS A total of 107 patients with overt hyperthyroidism were evaluated during the study period, 81 of whom were women (76%) with a mean age (±SD) of 46.9±16.1 years.

Clinical Features (Figure 1)

Of the 107 patients, 49 were classified as having mH (46%), 41 of whom were women (84%) 49±15 years of age; 37 were classified as MH (36%), 26 of whom were women (84%) 47±17 years of age; and 21 were classified as SH (20%), 41 of whom were women (84%) 41±17 years of age. Hyperthyroidism was regarded as de novo disease in 33 of 49 patients with mH (67%), 33 of 37 with MH (89%), and 19 of 21 with SH (90%). Hyperthyroidism was considered to be a relapse in 16 of 49 patients with mH (33%), 41 of 32 with MH (13%), and 2 of 21 with SH (10%). The SH group was significantly younger than the other groups, and a greater proportion of SH patients had their first (de novo) episode of hyperthyroidism ($P<0.05$ for both age and de novo episode as compared with patients who had mH and MH). The clinical features of the patients according to the severity of hyperthyroidism are shown in Figure 1. Here and elsewhere, percentages are rounded to an integer.

Causes of Hyperthyroidism (Figure 2)

Graves' disease was the cause of hyperthyroidism in 79 of the 107 patients (74%), and was significantly more frequent in patients with SH (n = 18, 86%) as compared with Graves' disease in the mH group (n = 31, 63%) and MH group (n = 30,

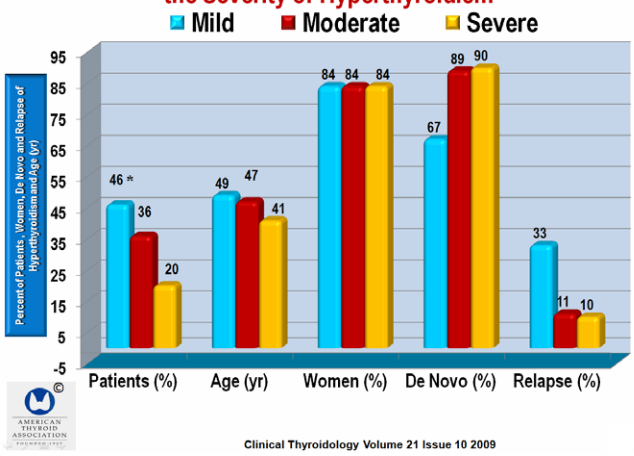

Figure 1. This figure shows the clinical features of 107 patients classified according to the severity of hyperthyroidism. *$P<0.05$ comparing mild hyperthyroidism versus moderate or severe hyperthyroidism. The data are derived from Table 1 in Iglesias et al.

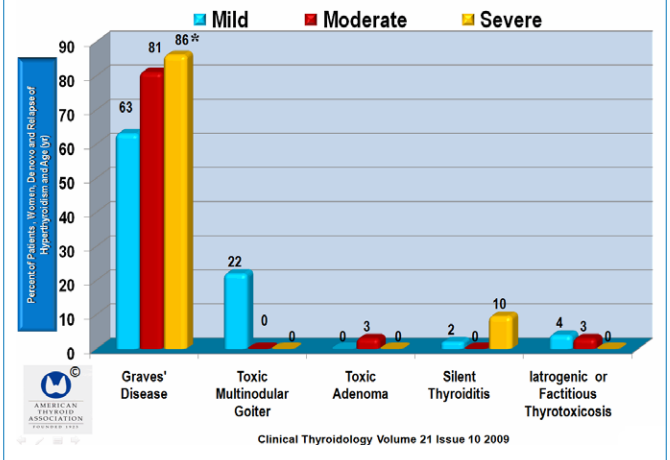

Figure 2. This figure shows the spectrum of causes for hyperthyroidism in this study. The data indicate the number of patients and percentage of each group of patients. *$P<0.05$ comparing mild and moderate hyperthyroidism groups with the severe hyperthyroidism group. The data are derived from Table 2 in Iglesias et al.

81%). None of the patients with SH had toxic multinodular goiter or thyroid adenoma. The other causes of hyperthyroidism are shown in Figure 2.

Signs and Symptoms (Figure 3)

The most common symptoms in the SH group were weakness, nervousness, dyspnea, and weight loss. Weight loss was 15.6±17, 5.8±11.7, and 8.6±9.7 lb (7.1±7.7, 5.8±5.3, and 3.9±4.4 kg) in the SH, MH, and mH groups, respectively. The heart rate and goiter grade were greater in the SH group as compared with the mH and MH groups (P<0.01). Atrial fibrillation was significantly more frequent in the SH group (16%) as compared with the mH (5%) and MH (0%) groups. However, there were no significant differences in the frequency of exophthalmos, goiter, or tremor in the SH group as compared with the mH and MH groups. Logistic-regression analysis found that the following three features were independently associated with SH: younger age (odds ratio [OR], 0.0.958 [95% confidence interval 95%CI, 0.923 to 0.995) P = 0.026), higher heart rate (OR, 1.03 [95% CI, 1.01 to 1.06, P = 0.013), and overall weakness (OR, 4.35 [95% CI, 1.48 to 12.78, P = 0.008])

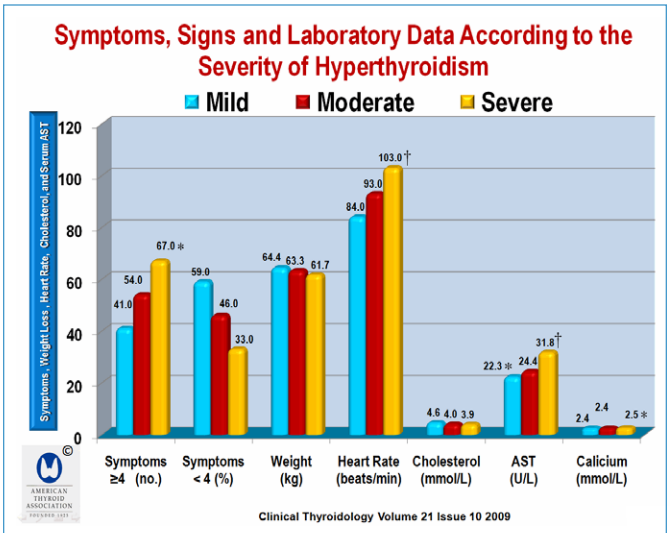

Figure 3. This figure shows the significant symptoms and signs of severe hyperthyroidism. †P<0.01 comparing heart rate in patients with mH and MH versus SH. *P<0.05 comparing four or more symptoms in severe hyperthyroidism versus mild and moderate hyperthyroidism. Patients with SH otherwise had similar laboratory findings as compared with the mH group, except for high AST (serum aspartate aminotransferase) (*P<0.01) and serum calcium levels (P<0.05). The data are derived from Table 3 in Iglesias et al.

Laboratory Data (Figure 4)

The only laboratory findings that were significantly different were TSH levels in the SH versus the mild hyperthyroidism group. The SH group had higher serum aminotransferase (AST) (P<0.01) and calcium (P<0.05) levels, and lower serum cholesterol and albumin concentrations (both P<0.05) as compared with the mH and MH groups. There was a positive association between serum FT_4 concentrations and heart rate (r = 0.309, P<0.05), alanine aminotransferase (r = 0.275, P<0.01), and TSH-receptor antibodies (r = 0.238, P<0.01), and a negative correlation with cholesterol (r = 0.313, P<0.01).

Treatment and Outcome (Figure 5)

Follow-up of more than 6 months was performed in 80 patients, 18 with SH (95%), 35 with mH (71%), and 27 with MH (73%). The duration of follow-up was 28.7±18.7 months for SH, 42.7±31.1 months for mH, and 49.8±43.3 months for MH (P = not significant). There were no significant differences in the therapy administered to the three study groups, including

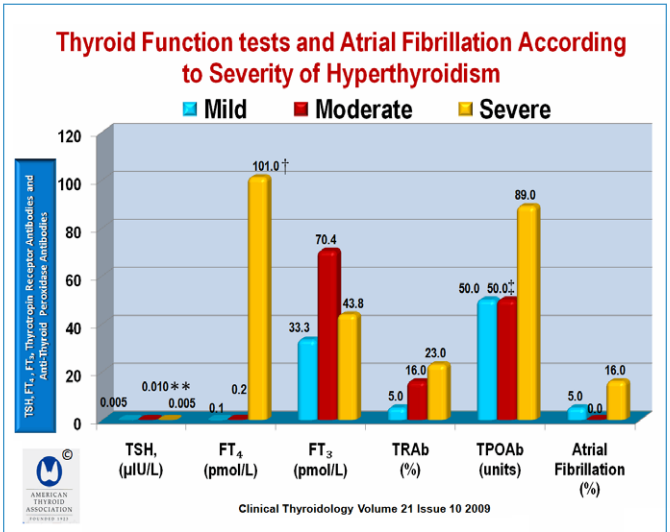

Figure 4. This figure shows thyroid-function test results according to severity of the hyperthyroidism. The mean serum FT_4 level was higher in the SH group than in the mH and MH groups. †P = 0.0001,* P<0.05, and **P = 0.002, comparing mH and MH groups with those with SH. There was a positive association between serum FT_4 levels and heart rate. Atrial fibrillation was significantly more frequent in the SH group as compared with the mH and MH (0%) groups. ALT = alanine aminotransferase; TPOAb = thyroperoxidase antibody; TRAb = TSH-receptor antibodies. The data are derived from Table 3 and the Results section in Iglesias et al.

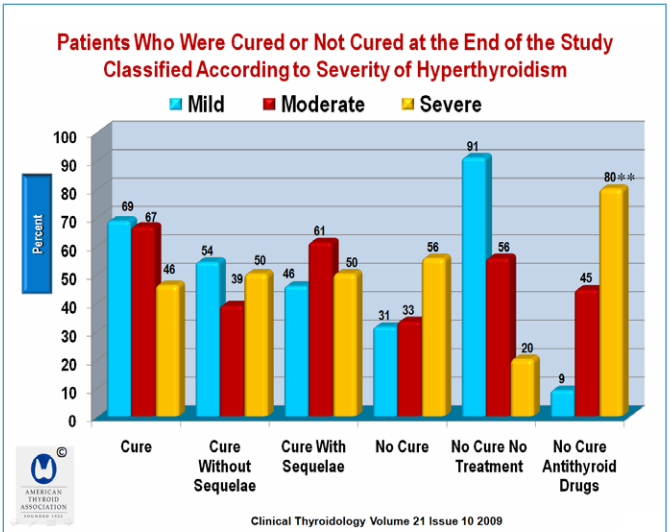

Figure 5. This figure shows the functional thyroid status and need for therapy in patients, who were cured versus those who were not cured at the end of the study. *P<0.01 comparing mH and MH groups versus the SH group. Cure without sequelae indicate post-radioiodine or postsurgical hypothyroidism and the need for L-T_4 therapy verus mH and MH groups, The data are derived from table 4 in Iglesias et al. There were no significant differences in the therapy administered to the study groups, including antithyroid drugs, radioiodine and surgery, nor were there differences in the subsequent rates of hypothyroidism following therapy.

the administration of antithyroid drugs, radioiodine, and surgery, nor were there differences in the subsequent rates of hypothyroidism following therapy in the three groups. However, patients with SH had a slightly lower cure rate as compared with the other two study groups. The only variable that was an independent predictor of cure was the serum FT_4 concentration (OR, 0.98[95% CI, 0.97 to 0.99 P<0.05); however, at the conclusion of the analysis, the thyroid functional status was similar among the three groups.

CONCLUSION Graves' disease is the most common cause of severe hyperthyroidism and is accompanied by more clinical signs and symptoms and laboratory abnormalities as compared with milder forms of hyperthyroidism

COMMENTARY

In this study, several features characterized the SH group: the majority had de novo hyperthyroidism (90%) as compared with 33% of patients with mH and 13% with MH who had de novo disease. The remaining patients had a relapse of hyperthyroidism. In addition, heart rates were higher and atrial fibrillation was more common in patients with SH as compared with patients who had less severe hyperthyroidism. Still, there were no differences in the type of therapy, cure rate, and time to achieve a cure. Logistic regression found that FT_4 was the only independent predictor of cure. The study was unable to find a difference in treatment, time to achieve a cure, and remission rate among patients in the three groups of hyperthyroidism. Although the symptoms of hyperthyroidism were more severe in patients with SH and MH, symptomatology was not used as a criterion for the diagnosis of severe disease.

The study by Iglesias based the severity of disease on the serum FT_4 levels, which are likely to provide one of the best criteria for severe hyperthyroidism, although the patient's presenting symptoms and cardiovascular manifestations generally provide a reliable set of features to identify patients with severe disease. Moreover severe myopathy and severe asthenia are also harbingers of severe disease. Still, as compared with younger patients, older patients with severe hyperthyroidism, are generally less likely to have tachycardia and tremor, and present with more weight loss (1). Moreover, cardiovascular manifestations of Graves' disease, especially atrial fibrillation, are common presenting symptoms in patients over 50 years of age (1-4).

In a comprehensive review Brent (1) advised antithyroid drugs, β-blockers, and propylthiouracil to block the conversion of T_4 to T_3. Most experienced endocrinologists rely on the symptoms of hyperthyroidism to provide an assessment of the severity of disease. Omitting the clinical presentations of signs and symptoms seems to be an important omission in stratifying the severity of disease.

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