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ANALYSIS OF HYPERTHYROIDISM REMISSION AFTER SUSPENSION OF THIONAMIDE WITH PROLONGED USE: A CROSS-CROSS-SET STUDY

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Abstract: Goals: evaluate the laboratory evolution of hyperthyroid patients, who used thionamides for at least 3 years, after discontinuing the drug. Methods: Cross-sectional study with an analytical component, developed between 2017-2018 in Limoeiro-PE- Brazil, using data from medical records in UPAE patients, on hormonal dosage values for one year after stopping the medication. **Results:** Among the 56 patients, women were 82.1%, age <40 years in 51.8%, methimazole as the drug used in 91.1%. Most patients had initial TRAb ≥ 3.5 IU/L (80.4%), TRAb in suspension <3.0 IU/L (80.4%) and TSH in suspension 3.0 IU/L in 58.9%. After discontinuation of the drug, 53.6% of patients remitted. Remission was present in 100% of those with initial TRAb <3.5IU/L and in 42.2% of those with initial TRAb ≥ 3.5IU/L. None of the patients with TRAb on drug suspension ≥ 3.0IU/L remitted. Of those who had TSH < 3.0 IU/L upon suspension, 13% remitted, while those with TSH 3.0 IU/L 81.8% achieved remission. **Conclusion:** remission of hyperthyroidism occurs in about half of patients who use antithyroid drugs for at least three years. The value of initial TRAb and TRAb and TSH after stopping the drug are also predictors of disease remission.
Keywords: Hyperthyroidism; Thionamides; Graves' disease.

INTRODUCTION

Thyrotoxicosis is a syndrome characterized by increased concentrations of thyroid hormones (T3 and T4) in the bloodstream. Its most common etiology is hyperthyroidism, which results from hyperfunction of the thyroid gland. [1].

The stimulus for excess hormone production can occur through different mechanisms, for example, through the autoimmune pathway as occurs in Graves' disease (GD) or through the development of self-functioning thyroid tissue, that is, capable of producing hormones without stimulation. of thyrotropin or thyroid-stimulating hormone (TSH), as occurs in toxic multinodular goiter (BMNT) and toxic adenoma (Plummer's disease)[2].

GD is the main cause of hyperthyroidism in regions where there is sufficient iodine in the diet, accounting for 60-80% of cases. The disease can appear at any age, but has a peak incidence between 20-50 years of age, with a predominance of females. [3]. It was first described in 1835 by Robert Graves as an autoimmune disease characterized by hyperthyroidism associated with goiter, ophthalmopathy and dermatopathy. [4].

The disease is the result of a combination of environmental and genetic factors. Regarding genetics, it is believed that HLA-DR polymorphisms, immunoregulatory genes such as CTLA-4, CD25, PTPN22, FCRL3 and CD226, as well as TSH receptor genes (TSH-R), help in the onset of the disease, while HLA-DRB1 would have a protective effect. Environmental issues would be related to factors such as stress, which appears to induce a state of immunosuppression through the neuroendocrine action of cortisol, favoring the activation of autoimmunity [5].

Other factors may be linked to the onset of GD, for example, increased iodine intake has been associated with the disease [6]. Studies suggest that the main incidence in women occurs due to exposure to estrogen, and this hormone can be considered a risk factor, as it is responsible for increasing immunological reactivity [7].

The most common clinical manifestation of GD is a diffuse goiter of variable size with a firm consistency, present in 90% of patients under 50 years of age. The most frequent systemic symptoms include hyperactivity, irritability, dysphoria, fatigue and weakness, sinus tachycardia, palpitations, insomnia

and weight loss. These symptoms are present in around 50% of patients. As we age, loss of weight and appetite outweigh other symptoms. The skin is generally hot and moist, and the patient may complain of excessive sweating, heat intolerance and experience palmar erythema, urticaria, itching and hyperpigmentation, the latter only in more severe cases [8].

The concentration of estradiol is increased by the greater extragonadal conversion of testosterone into estradiol, a fact that generates gynecomastia, decreased libido and erectile dysfunction. In women, the presence of oligomenorrhea or amenorrhea is common, due to similar hormonal changes. Gastrointestinal peristalsis is accelerated, which can lead to diarrhea and, less frequently, steatorrhea. [9].

Graves' ophthalmopathy is a specific ocular sign of the disease and is present in approximately 50% of patients. Its most frequent signs are eyelid retraction, resulting from sympathetic hyperactivity, and periorbital edema. About a third of patients also exhibit proptosis and 5-10% have diplopia[10].

Dermopathy is present in less than 5% of patients. It can result from trauma and is generally located on the dorsum of the foot or in the pre-tibial region. The lesion is characterized by a reddish or purple plaque with an orange peel appearance and, in most cases, is asymptomatic. Itching and local pain rarely occur. Thyroid acropathy is present in less than 1% of patients with the disease and is characterized by clubbing of the fingers. It is usually closely related to thyroid dermopathy[11].

The diagnosis of GD is simple when the patient presents biochemically confirmed thyrotoxicosis associated with diffuse goiter on palpation, ophthalmopathy and a personal or family history of autoimmune disorders. The presence of diffuse goiter associated with ophthalmopathy and dermopathy is sufficient to confirm the diagnosis [12].

When the clinical picture is not so evident, the diagnosis can be made by measuring TSH and free T4, which will show decreased and increased concentrations, respectively. In cases of subclinical disease, free T4 levels may be within normal limits and TSH levels may be reduced, requiring T3 measurement, which may be increased. [13].

Associated with hormones, the measurement of anti-TSH-R antibodies (TRAb) is almost always positive, and its detection, when associated with thyrotoxicosis, is diagnostic for the disease. [8]. Complementary tests may be necessary for differential diagnosis with other thyrotoxicosis when the clinical picture is not so evident. The diagnosis can be established by thyroid scintigraphy, which differentiates diffuse and high uptake of Graves' disease from destructive thyroiditis, ectopic thyroid tissue and factitious thyrotoxicosis. Scintigraphy is the preferred complementary test for differential diagnosis, although TRAb determination can also be used to assess autoimmune activity. [14].

The therapeutic approach to GD hyperthyroidism consists of symptomatic control with beta-blockers and reduction of thyroid gland hormone synthesis through administration of thionamides, radioactive iodine or surgery. [15]. Regardless of the treatment chosen, initial monitoring includes periodic clinical surveillance and hormone measurement (free T4, TSH and, when necessary, T3). It is important to know that TSH may remain suppressed for several weeks after normalization of free T3 and T4 fractions. [16].

Drug treatment with drugs that block hormone synthesis – thionamides – is the main choice, with Methimazole (Tapazol®) as the first option, which inhibits the production

of thyroid hormones in follicular cells, its initial dose is 10-30 mg/day and After 6-8 weeks, depending on the patient's clinical and hormonal control, a maintenance dose of 5-10mg/day is instituted. Another available drug is Propylthiouracil (PTU) with an initial dose of 200-400 mg/day and after 6-8 weeks, also depending on the patient's progress, a maintenance dose of 50-100mg/day is established. This drug in higher doses has the additional action of reducing the peripheral transformation of T4 into T3 and therefore may be the choice for cases of thyrotoxic crisis. [17].

The most feared effect of both drugs is agranulocytosis, which occurs, most of the time, in the first 90 days of treatment. Fever and odynophagia are frequent manifestations that must lead to a leukocyte count. Hepatotoxicity occurs in 0.1-0.2%. PTU is associated with the occurrence of allergic hepatitis, with elevated transaminases and massive hepatic necrosis. Methimazole is rarely related to a cholestatic process. Vasculitis is more present with the use of PTU, including ANCA positive vasculitis.

Other side effects present are: allergic reactions, arthralgias, nausea, thrombocytopenia, aplastic anemia, hypoprothrombinemia, hypoglycemia and pancreatitis[18].

It is recommended that drug therapy lasts 12-24 months, a period in which disease remission occurs in 30% to 50% of cases. If this does not occur, the patient must undergo another form of definitive therapy, be it the use of radioactive iodine or thyroidectomy, as GD is a potentially serious disease with high morbidity. However, in some cases, due to various factors, the use of thionamides is not discontinued, and the drugs are used chronically. [19].

This work aims to evaluate the laboratory behavior of hyperthyroid patients, who used thionamides for at least three years, after stopping the use of the drug.

METHODOLOGY

A cross-sectional study with an analytical component was carried out. The study population was made up of hyperthyroid patients treated at the endocrinology outpatient clinic at UPAE in Limoeiro-PE who used thionamides for three or more years and who had their use of the drug suspended due to their thyroid function being under control.

Data collection took place during the months of April and May 2018, a period in which patients were informed about the research objectives and invited to participate by signing the Free and Informed Consent Form (TCLE).

The data collected from the medical records refers to sociodemographic characteristics, time of drug use, drug used and the following laboratory tests: TSH when stopping the drug and after 3,6,12 and 18 months of suspension, free T4 when stopping the drug and after 3, 6, 12 and 18 months after suspension, T3 when the drug was suspended and after 3, 6, 12 and 18 months after suspension and TRAb when the disease was diagnosed and when the drug was suspended.

The collected data were stored and organized in an Excel 2010 Spreadsheet in order to be statistically analyzed using SPSS 13.0 Software (Statical Package For the Social Sciences). The tests were applied with 95% confidence, using Fisher's Exact Test and Chi-Square Test for categorical variables and the Kolmogorov-Smirnov Normality Test for quantitative variables. The results were displayed in tables with their respective absolute and relative frequencies. Numerical variables are represented by measures of central tendency and measures of dispersion. Comparison with more than two groups was performed using the Student t Test (Normal Distribution) and Mann-Whitney (Non-Normal).

The significance level adopted was p<5% (p<0.05). This work was approved by the Ethics and Research Committee on Human Beings of ``Faculdade Pernambucana de Saúde`` (FPS), under opinion number 2,597,395.

RESULT

The total number of UPAE patients analyzed during the research period was 56, all of whom had Graves' Disease. The sample consists of 46 (82.1%) female patients and 10 (17.9%) males. Of the total number of patients, 29 (51.8%) are < 40 years old and 27 (48.2%) are ≥ 40 years old. The mean age was 39.8 years (SD 5.2). Regarding the drug used for treatment, 51 (91.1%) patients used Methimazole and 5 (8.9%) used Propylthiouracil. The average time patients had been using the drug, before suspension, was 41.8 months (SD 4.6). In relation to the initial TRAb value at the diagnosis of the disease, 11 (19.6%) patients had TRAb<3.5 IU/L and 45 (80.4%) had TRAb≥ 3.5IU/L. Regarding TRAb when suspending the drug, 45 (80.4%) presented a value < 3.0UI/L, while 11 (19.6%) ≥ 3.0UI/L. Regarding the TSH value when the drug was discontinued, 23 (41.1%) had TSH <3.0UI/L, while 33 (58.9%) of the patients had a TSH value ³3.0UI/L. Finally, 30 (53.6%) patients achieved remission of Graves' Disease.

Among female patients, 27 (58.7%) experienced remission. In contrast, in male patients, 3 (30%) remitted. In patients with It was verified that: < 40 years old, 15 (51.7%) presented remission. In patients aged ≥ 40 years, 15 (55.6%) achieved remission. Regarding the drug used, of the patients who used Methimazole, 29 (56.9%) remitted and of those who used Propylthiouracil, only 1 (20%) achieved remission. It was seen that, of the 56 patients, those with initial TRAb <3.5UI/L achieved remission in 100% (11 patients), while of the patients with initial TRAb ≥ 3.5UI/L, 19 (42.2%) remitted. Regarding the TRAb value when the drug was discontinued, of the patients with TRAb<3.0 IU/L, 30 (66.7%) experienced remission. However, no patient with TRAb≥ 3.0UI/L showed remission. Regarding the TSH value, 27 (81.8%) of those who presented remission had TSH ³ 3.0 IU/L. In contrast, only 3 (13%) of those with TSH <3UI/L experienced remission. The average TSH value when the drug was discontinued in patients who remitted was 4.33UI/L. The variables of age (p= 0.774), sex (p=0.162) and the drug used (p=0.172) were not relevant to remission. However, the initial TRAb value and upon discontinuation of the drug and the TSH value upon discontinuation were relevant for disease remission, respectively, at p=0.001, <0.001 and <0.001.

Of the total sample, 26 (46.4%) presented recurrence. Within this group, relapse occurred within the first 6 months of drug discontinuation in 11 (42.3%) and within 12 months in 15 (57.7%). Among those who had TSH < 3.0 IU/L after 6 months, 72.2% had a relapse and 80% of those who had TSH < 3.0 IU/L after 12 months developed a relapse.

DISCUSSION

The analysis of hyperthyroidism remission after the suspension of long-term thionamides is of fundamental importance as it highlights the main variables that influence the remission process. Therefore, knowledge of these variables makes appropriate work-up possible, consequently minimizing the adverse effects and costs generated by prolonged use of medications.

In the present study, a total of 56 patients met the determined inclusion criteria. According to statistical analysis, the female sex was predominant, accounting for 82.1%, a fact that is corroborated by a study carried out in Great Britain with 2779 adults in which the rate of women with hyperthyroidism is around 10 times higher than the male rate [20].

Furthermore, another study carried out on patients with Graves' Disease at ``Hospital Universitário Clementino Fraga Filho`` (HUCFF) showed that of the 107 patients evaluated, 93 were women and 14 were men, a factor similar to that found in our study. It is believed that this higher frequency in females could be due to the influence of estrogen on immune system cells, particularly B cells. [21].

The average age of patients with Graves' Disease found in our study was 39.8 years, similar to what was found in a study carried out at the Hospital de Santa Maria, in Lisbon, where the average age of patients with the disease was 38.48 years24. This relationship can be explained by the fact that estrogen also has the ability to stimulate the production of TSH. As this age group, in general, is related to the climacteric period, there is a reduction in estrogen levels, triggering hyperthyroidism[22,23].

In our study we found that the variables age and sex were not relevant for disease remission p= 0.774 and p= 0.162, respectively. On the other hand, a survey carried out with 536 patients with Graves' Disease at the Queen Elizabeth Hospital, United Kingdom, showed that patients aged < 40 years have less chance of disease remission (32,6%)[21]. In the same study, it was found that male sex is associated with failure to respond to medication and a higher rate of relapse. However, we believe that this difference between the sexes is not very significant given the small number of male patients. Regarding the importance of age in the outcome, we believe that this difference found between studies occurs due to our sample having a similar age distribution, presenting a standard deviation of 5.2.

The drug most used by patients in the present study was methimazole and the type of medication used was not found to be relevant to remission (p= 0.172). It is believed that the preference for the use of methimazolse is due to the great advantage of the single daily dose, dose-dependent side effects (rare with dose <20 mg/day) and potential for less severe hepatotoxicity [17].

In the present study, it was analyzed that after 12 months of drug suspension, 53.6% of patients showed normal thyroid hormone levels, configuring remission. In another research carried out at HUCFF, similar to ours, disease remission was observed in 58 (45.7%) patients [25]. The disease remission process in patients treated for at least 6 months would occur since such drugs are capable of blocking hormonal synthesis and, according to some researchers, capable of altering the course of the underlying autoimmune process. [17].

The value of the anti-TSH receptor antibody was shown to be one of the main factors related to disease remission. When Graves' disease was diagnosed, the TRAb value proved to be quite relevant, since all patients who had a value < 3.5 IU/L achieved remission of the disease and only 42.2% of patients with a value ³ 3.5 IU/ L had remission. However, a study carried out at the endocrinology institute of the university of Pisa, Italy, carried out with 306 patients demonstrated that the remission rate of hyperthyroidism occurred in only 46.6% of patients with TRAb<3.0 IU/L while values ³ 3.0 UI/L achieved remission in only 15%[26].

We believe that the different results can probably be justified by the different methodologies used to detect antibodies and the difference in the population studied, with different genetic and external factors, for example, iodine intake. Studies show that iodine deficiency hinders the stimulating action of low TRAb titers, and in these cases, higher antibody titers are present during the course of the disease. [27]. Taking this factor into account, it is known that European countries, such as Italy, have a deficiency in the intake of this ion, which may explain the low remission

of the disease in these regions. While, in Brazil, there is an excess in iodine intake [28].

The TRAb value after discontinuation of the drug was also important, as none of the patients who had a value ³ 3.0 IU/L had remission. However, 66.7% of those with a value < 3.0 IU/L experienced remission. This ability to predict the outcome was also found in a meta-analysis of 18 published studies that found an association between high serum levels of TRAb after treatment and a higher rate of disease recurrence [29].

The patients in our study had an average TSH of 3.17 IU/L, after one year of stopping the drug. Just like patients in a similar study conducted in Paris, France at the St. Antoine faculty of medicine, where patients averaged TSH 3.3 UI/L[30]. The TSH value also influences the remission rate of Graves' disease, in our study 81.8% of those who remitted had TSH ³ 3 UI/L. This is consistent with the response to treatment, since high levels of TSH suppress the production of thyroid hormones, resulting in euthyroidism. [17].

Some studies have shown that reduced TSH levels after approximately one month of stopping the drug are related to disease recurrence. [30,31,32]. As it was seen in our study, in which among patients who had a relapse of the disease within 6 months, 72.7% had TSH < 3.0 IU/L and among those who had a relapse within 12 months, 80% had TSH <3.0 IU/L.

We conclude, based on our findings, that remission of hyperthyroidism occurs in approximately half of patients who use antithyroid drugs for at least three years. We also verified that the initial TRAb value is an important determinant for this remission, considering that this antibody is the main causative agent of the disease. The value of TRAb and TSH after stopping the drug are also predictors of treatment success. However, more studies are needed to corroborate or not the results found.

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ILLUSTRATIONS

Variables	Remission		p-value
	Yes	No	
	n (%)	n (%)	
Age			
< 40	15 (51,7)	14 (48,3)	0,774 *
≥ 40	15 (55,6)	12 (44,4)	
Gender			
Female	27 (58,7)	19 (41,3)	0,162 **
Male	3 (30,0)	7 (70,0)	
Drug			
Methimazole	29 (56,9)	22 (43,1)	0,172 **
Propylthiouracil	1 (20,0)	4 (80,0)	
Work.: Initial diagnosis			
< 3,5	11 (100,0)	0 (0,0)	**0,001** *
≥ 3,5	19 (42,2)	26 (57,8)	
Work.: When discontinuing the drug			
< 3,0	30 (66,7)	15 (33,3)	< **0,001** *
≥ 3,0	0 (0,0)	11 (100,0)	
TSH			
< 3,0	3 (13,0)	20 (87,0)	< **0,001** *
≥ 3,0	27 (81,8)	6 (18,2)	

Table 1: Factors associated with remission of Graves' disease after at least three years of antithyroid drug use. Recife 2018.

(*) Chi-Square Test (**) Fisher's Exact Test