

CASE REPORT**Remission of Graves' Disease in a female patient with isolated methimazole-dependent febrile agranulocytosis.**

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ABSTRACT

I report the case of a patient affected by Graves' Disease and treated with an antithyroid drug such as methimazole. During the drug treatment she presented a methimazole dependent agranulocytosis and the drug was immediately withdrawn. Amazingly, thyroid hyperstimulation vanished during withdrawal of anti-thyroid therapy and the patient underwent a remission. The role that stress factors may exert on the autoimmune process directed against the thyroid gland is discussed.

Key-words: Graves' disease – thyroid – autoimmunity – methimazole - agranulocytosis

INTRODUCTION

Thyrotoxicosis is a common endocrine disorder. It affects mainly women and is approximately five times more common in females than in males. Usually the patients are treated with antithyroid drugs such as methimazole and carbimazole. A rare and potentially fatal complication of the therapy is the agranulocytosis, ranging from 0.3% to 0.6%. The stress factors seem to be important to trigger the onset of the disease. In literature no role is usually reported of the stress such as a

possible cause of hyperthyroidism recovery. We describe an unusual remission of Graves' Disease following the onset of a febrile agranulocytosis induced by methimazole.

CASE REPORT

In March 2008 we observed a 52 years old female patient with tachycardia and fine tremor. Elevated free triiodothyronine (FT3), free thyroxine (FT4) and TSH receptor antibodies (TRAbs) with suppressed thyrotropin (TSH) were observed. Anti-thyroglobulin and anti-thyreoperoxidase was slightly positive and no significant time dependent modifications were observed. Thyroid scintigraphy showed a diffuse ¹³¹I distribution with an increased uptake. No ophthalmopathy was present. The thyroid ecography showed a slight increase of volume, a hypoechoic gland with an increased vascularization at Doppler study. The patient started a methimazole (MMI) treatment with 20 mg/die, after progressively reduced to 15 and 10 mg.

Suddenly, in June, after two months of MMI treatment, the patient showed sore throat and fever (temperature, 39,5°C), the blood cell count indicated a marked reduction of white blood cells (WBC) and neutrophils (N), compatible with the diagnosis of an isolated agranulocytosis. The values of the other blood cells were normal. The MMI treatment was immediately withdrawn and the patient admitted to hospital. No hepatic and kidney failure was observed. Anti-nuclear antibodies were negative while anti-granulocyte antibodies was not evaluated. The fever and the sore throat solved after three days of antibiotic and antimycotic treatment and a progressive improvement of WBC and N was observed. No steroid treatment was started. After nine days the antibiotic treatment was withdrawn and the patient was discharged. We tested every ten days the FT3, FT4 and TSH in order to identify the hyperthyroidism relapse. Amazingly, the hormonal status and the TRAbs levels showed a progressive normalization without MMI treatment (Table 1). The patient did not attend the subsequent clinical controls (she lives in a rural area), but did not refer manifestations indicative of hyperthyroidism relapse in the following 3 months. In consideration of the impossibility to use antithyroid drugs, radiometabolic treatment was recommended in case of possible future relapse of hyperthyroidism.

DISCUSSION

Many papers discuss the importance of the stress to induce the onset or the worsening of the GD (1). On the contrary, in the case here reported, the stress dependent on a febrile agranulocytosis, might represent an unusual cause of GD remission.

Self-limited transient forms of GD are described after delivery, surgery of Cushing's disease, the withdrawal of antithyroid drugs or such as the spontaneous transient Graves' thyrotoxicosis (2). But the clinical characteristics could not assign this patient to one of these categories. Indeed, the long-lasting duration of MMI withdrawal guaranteed that the resolution of the hyperthyroidism was not dependent upon a drug effect. However, other factors, such as the TRAbs levels, the age and the goiter size, indicated that our patient was more prone to undergo a remission of hyperthyroidism, according to Vitti et al (3).

Table 1. Laboratory values detected at different times and laboratory normal ranges (n.r.). In bold the values at the moment of the hospital admission and MMI suspension. Not done (n.d.)

	01/03/08	21/03	25/05	12/06	26/06	15/07	26/08	n.r.
FT4	2.65	2.22	1.5	1.78	1.14	1.19	1.45	0.93-1.71 ng/dL
FT3	16.17	10.16	5.5	3.9	4.11	4.07	4.4	3.1-6.8 pmol/L
TSH	0.02	0.02	0.09	0.13	0.12	0.26	0.65	0.27-4.2 mu/L
TRAbs	20.8	n.d.	n.d.	n.d.	1.1	n.d.	1.0	<10 IU/L
WBC	n.d	5.0	4.2	1.5	5.6	4.8	5.0	4.0-11.0 10 ³ /mm ³
N	n.d	47.0	48.5	4.0	48.6	47.9	51	50-80 %

Usually, an immunosuppressive mechanism of the antithyroid drugs has been hypothesized to explain the remission in GD (4). Anyway, many evidences does not support this point of view, evidencing that the remission (secondary to TRAbs normalization) in GD is independent of dose, kind of antithyroid drug or surgical treatment (5). The restored euthyroidism, independently if secondary to the drug or surgical treatment, seems to be the main factor inducing the remission of GD, breaking the vicious circle existing between autoimmunity and hyperthyroidism (6).

It is well known that a significant stress, such as a sepsis, can induce a decrease in thyroid hormone bioavailability (7) and a severe immunosuppression (8). Conceptually, the decreased bioavailability, mainly, of FT3 and the immunosuppression are, theoretically, able to induce the normalization of TRAbs with consequent remission of the autoimmune process and hyperthyroidism in GD.

Moreover, in consideration that antithyroid drug-induced agranulocytosis and aplastic anemia are dependent on autoantibodies directed, respectively, against granulocyte and bone marrow (4), another possible hypothesis is that a similar autoimmune process could suppress the source of TRAbs responsible of the hyperthyroidism.

CONCLUSIONS

On the basis of the reported findings, it is tempting to speculate that the stress of the febrile agranulocytosis could have played an important role in disrupting the vicious circle between hyperthyroidism and autoimmunity in this patient. Then, should we consider that stress factors may potentially be able to induce opposite (negative or positive) effects on the autoimmune processes affecting the thyroid gland?

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