Methimazole-Induced Agranulocytosis in a Mother and her Young Daughter; the Possible Role of Genetic Factors in the Development of Methimazole-Induced Agranulocytosis

Bahrami A.

Division of Endocrinology and Metabolism, Department of Medicine, Tabriz University of Medical Sciences, Tabriz, I.R.Iran

Agranulocytosis is a rare but life-threatening side effect of thionamides. Some data indicate that the susceptibility to thionamide-associated agranulocytosis in patients with Graves’ disease has a genetic basis. The case histories of a mother and her daughter with Graves’ disease who developed agranulocytosis with methimazole are presented here. It seems reasonable to avoid the use of thionamide derivates in hyperthyroid relatives of patients who have had thionamide-induced agranulocytosis.

Key words: Thionamide, Methimazole, Agranulocytosis, Genetic factors

Introduction

Agranulocytosis is a rare but most serious adverse effect of thionamide drugs. It has been reported to affect 0.3%-0.6% of patients treated with thionurea-derivatives.⁴⁻⁶ Although the exact responsible mechanism is unknown, it is thought to have an autoimmune basis.⁷⁻⁹ It has been suggested that antineutrophil cytoplasmic antibodies play an important role in its pathogenesis.¹⁰⁻¹⁴ Factors or clinical circumstances that might predispose to thionamide-associated agranulocytosis remain largely unknown. An HLA-linked genetic factor is associated with susceptibility to methimazole-induced agranulocytosis. A strong positive association between HLA class II genes and methimazole-induced agranulocytosis has been reported in Japanese patients with Graves’ disease suggesting that cellular autoimmunity can be involved in its development.¹⁵ Thus, it seems reasonable to avoid antithyroid drug therapy in hyperthyroid relatives of patients who have had thionamide-associated agranulocytosis. Described here are the case-histories of a mother and her daughter with Graves’ disease who developed agranulocytosis with methimazole.

Case history

Case One:
A 51-year old female, presented with a three-month history of palpitation, tremor, weight loss of 12kg, restlessness, excessive
sweating, polydipsia, heat intolerance and generalized pruritus. There was a four-year history of hypothyroidism in one of her sisters. Physical examination revealed tachycardia, fine tremor, bounding pulses, warm and moist skin, onycholysis, bilateral lid retraction and mild right-sided proptosis. She had a diffuse thyroid enlargement of about 3-times the normal size with an audible bruit over it. Laboratory investigations showed a fasting plasma glucose of 94 mg/dL, white blood count of 7100/µL (66% PMN), serum thyroxine level (T₄) of 18.5 µg/dL, triiodothyronine (T₃) of 460 ng/dL, T₃-resine uptake of 42% and serum TSH level of 0.1 µU/mL. Thyroid scan showed high and diffuse uptake. Methimazole was started with a dose of 10 mg three times daily and propranolol 40 mg twice daily. She was instructed to discontinue the drug and contact a physician immediately if fever, chills, sore throat or other symptoms of infection developed. Three weeks after initiation of methimazole therapy, she presented to the endocrine clinic with fever, shaking chills, painful mouth ulcers and odynophagia of two days duration. Upon presenting she was febrile and toxic. Her body temperature was 39.8 C°. Examination revealed multiple mouth ulcers and extensive pharyngeal exudates. Immediate white blood count was ordered and found to be 740/µL with 195/µL granulocytes. She was admitted to hospital, where she found to be febrile and toxic. There were multiple oral ulcers and exudative pharyngitis. Treatment with broad spectrum antibiotics, IV fluids and dexamethasone resulted in her gradual improvement and bone marrow recovery. She was discharged from hospital 11 days later. Her while brood count at the time of discharge was reported to be 3960/µL with 40% PMN cells.

**Discussion**

The exact mechanism of the thionamide-induced agranulocytosis is not clear.²⁻⁶ Some believe that thionamides exert a direct cytotoxic effect on the bone marrow,¹,16 but recent studies suggest that an immune phenomenon may be involved.⁷⁻⁹ Antineutrophil antibodies or lymphocyte sensitization to antithyroid drugs can be found in patients suffering from thionamide-induced agranulocytosis.¹⁰⁻¹⁴ It has been suggested that these antibodies play an important role in the pathogenesis of agranulocytosis through direct cytotoxicity or growth inhibition of progenitor cells.¹⁷ Factors or clinical circumstances that might predispose to thionamide-induced agranulocytosis remain largely unknown. Cooper et al. investigated the role of patient age, dosage and type of thionamide used, on development of agranulocytosis.¹₈ Their results showed that low doses of methimazole

**Case Two:**

A 27 year-old female, the daughter of the first case, presented with symptoms and signs of thyrotoxicosis. She was seen in a private clinic where she was found to have tachycardia, fine tremor, diffuse goiter, and bilateral mild proptosis and periorbital edema. Laboratory investigations showed normal CBC, serum T4 of 21 µg/dL, T₃ of 398 ng/dL, T₃ resin uptake of 38% and serum TSH of 0.07 µU/mL. Methimazole was started with a daily dose of 45 mg (15 mg three times) and propranolol was prescribed 40 mg twice daily. Twelve days after initiation of antithyroid therapy, she developed fever, chills, sore throat, and oral ulcers. She was seen by a general physician who prescribed penicillin. She remained symptomatic despite penicillin injections. A white blood count was ordered and found to be 450/µL with 148 granulocytes. She was admitted to hospital, where she found to be febrile and toxic. There were multiple oral ulcers and exudative pharyngitis. Treatment with broad spectrum antibiotics, IV fluids and dexamethasone resulted in her gradual improvement and bone marrow recovery. She was discharged from hospital 11 days later. Her white blood count at the time of discharge was reported to be 3960/µL with 40% PMN cells.
(< 30 mg/day) were associated with a lower incidence of agranulocytosis than higher doses of MMI or conventional doses of PTU. The HLA class II oligotyping data suggest that the susceptibility to thionamide-induced agranulocytosis in patients with Graves’ disease has a genetic basis.

In an effort to determine the possible role of genetic factors in the development of methimazole-associated agranulocytosis in patients with Graves’ disease, Tamai and his co-workers conducted a case-control study in Japanese people, in which they examined the association between HLA class II genes and thionamide-induced agranulocytosis. Their results showed a strong association between DRB1*08032 allele and susceptibility to methimazole-induced agranulocytosis. They concluded that this specific HLA class II allele was directly involved in the development of agranulocytosis in Japanese patients. Although the results of this study confirm the existence of a genetic predisposing factor that may allow the prediction of the thionamide-related agranulocytosis such a finding is of limited clinical utility for the following reasons: 1) HLA typing is impractical in all patients with Graves’ hyperthyroidism who are candidates for thionamide therapy in terms of time and cost; 2) The result indicates susceptibility only in Japanese people and it might not be applicable to other ethnic groups; and 3) Positive result for a specific allele does not imply that methimazole should be withheld in patients with Graves’ hyperthyroidism, because of sufficiently low frequency of agranulocytosis in patients with these alleles. It was not possible for us to analyze HLA class II genes for polymorphisms at DNA level in our patients.

In conclusion due to the obscurity of its etiology, at present, it is impossible to predict which patient may be at risk for development of thionamide-associated agranulocytosis. Since, the HLA class II oligotyping data indicate that the susceptibility to thionamide-induced agranulocytosis in patients with Graves’ disease has a genetic basis, it seems reasonable to avoid the use of thionamide derivates in hyperthyroid relatives of patients who have had thionamide-induced agranulocytosis.

References


