GRAVES' DISEASE IN ASSOCIATION WITH AUTOIMMUNE THROMBOCYTOPENIC PURPURA — A CASE STUDY

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SYNOPSIS

The association between thrombocytopenia and Graves' disease has been reported but this condition is rare. A young girl with this disease, presenting with acute autoimmune thrombocytopenic purpura, is the first case to be reported in Singapore. The literature on the subject is reviewed. Etiology of this association is unclear to date though an autoimmune basis is favoured. Mechanism of the disease is postulated.

INTRODUCTION

Thyrotoxicosis and thrombocytopenia are, by themselves, fairly common diseases.

Tunbridge et al, in 1977, indicated a prevalence of 1.9% in females and of 0.2% in males, of overt thyrotoxicosis (1). It is now virtually certain that the excessive output of thyroid hormones is due to abnormal stimulation of the thyroid gland by circulating immunoglobulins. Current view considers that Graves' disease is due to a genetically determined disorder of immunological stability which allow B lymphocytes to proliferate and secrete these antibodies, possibly because of failure of either suppressor T lymphocyte function or anti-idiotype antibody production (2).

Autoimmune thrombocytopenic purpura is frequently referred to as Idiopathic thrombocytopenic purpura (3). Autoimmune thrombocytopenic purpura (AITP) is presently a diagnosis made by exclusion although an antiplatelet factor consisting of an immunoglobulin G (IgG) type antibody has been demonstrated (4). It is now generally accepted that, for some reason, platelets become coated with IgG and/or C^3 complement and that these opsonised platelets are then phagocytized by reticuloendothelial cells in the spleen and and liver (5).

Although thrombocytopenic purpura associated with Systemic Lupus Erythematosus and some other autoimmune diseases is well known (6), thrombocytopenic purpura as a presenting symptom of Graves' disease is rarely encountered.

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The first description of this association is generally attributed to Jackson in 1931 who reported a case of acute haemorrhagic purpura with exophthalmic goitre. The author mentioned a reduction in number of platelets as one of the criteria for the diagnosis of haemorrhagic purpura but a count was not recorded (7). Following this, there has been scattered reports over the years describing this association (8-26). It was not till 1974 when the existence of specific humoral agents for both Graves' disease and thrombocytopenic purpura was demonstrated that there was actual proof that both diseases do in fact occur together (18).

In 1978, Herman et al, reviewed the past literature and found 49 cases of this association. Of these, only 29 were described in sufficient detail so as to exclude known causes of thrombocytopenia (22). To date, a further 9 cases has been recorded. It can therefore be seen that this is a rare condition. Such a case, believed to be the first reported in local literature, of a young girl presenting with thrombocytopenia and found to be thyrotoxic, is described.

CASE REPORT

A 11 year old Chinese girl, first presented on 21 January 1983 with a history of easy bruising and petechiae over the trunk and lower limbs, for one month duration. She was previously well. The petechiae appeared abruptly and increased progressively with time. There was no history of any recent illness, drug ingestion or bleeding disorders. There was no family history of significance. There were no classical thyrotoxic symptoms.

Initial examination revealed a normal looking girl, 153 cm tall and weighing 46 kg (both height and weight exceeding the 97th percentile for her age). There were widespread petechiae and bruises present over body and extremities. In addition, petechiae as well as haemorrhagic bullae on the buccal mucosa was noted. The liver was just palpable and the spleen was not palpable. Cardiac and respiratory systems were normal. Resting pulse rate was 100/minute. There were fine tremors of both hands and the palms were noted to be abnormally moist. Further examination revealed a diffusely enlarged thyroid gland in which a bruit could be auscultated. The patient's nervous system and mental state was normal.

Investigations done included a full blood count in which the Haemoglobin level was 9.7%. Platelet count on admission was 5,000/mm^3. There was relative lymphocytosis (42% of a leukocyte count of 7,900/ul). Bone marrow aspirate showed increased megakaryocytes with iron depletion. The thyroid function tests confirmed the diagnosis of thyrotoxicosis. Serum thyroxine (T4) levels were raised — 24.4 ug/dl (Normal range = 4.6 to 12 ug/dl). Serum T3 resin uptake was increased — 174 ng/dl (Normal range = 77 to 122 ng/dl). Free thyroxine index was 40 (Normal range = 4.6 to 11.6). In addition, thyroid microsomal antibodies were positive, as were thyroglobulin antibodies — with a titre of 1 in 1600. Laboratory identification of thyroid stimulating immunoglobulin was not avilable. Other investigations were within normal range. Erythrocyte sedimentation rate was 20 mm/hr. Serum for LE cells, parietal cell and smooth muscle cell antibody were negative. Rose Waaler test was negative. PT/PTT, urine examination and the electrocardiogram were all normal.

Diagnosis of Graves' disease with thrombocytopenia was made.

TREATMENT AND PROGRESS

The patient was started on Prednisolone 20 mg 6 hourly on the 2nd hospital day. The response was dramatic — the platelet count rising to 50,000/mm^3 on day 5, 140,000/mm^3 on day 6 and to 500,000/mm^3 at discharge. Prednisolone was tailed down gradually. Carbimazole was started on laboratory confirmation of thyrotoxicosis.

There was symptomatic improvement and the patient was discharged on 5 February 1983. There was no more clinical evidenece of thrombocytopenia. Medication on discharge was Prednisolone 10 mg twice daily and Carbimazole 5 mg thrice daily.

Other investigations which were done after treatment was started included: Direct Coomb's test which was weakly positive (4/2/1983) and antiplatelet antibody was demonstrated to be weakly present (on 18/2/83).

DISCUSSION

Presence of a diffuse toxic goitre virtually confirmed the diagnosis of Graves' disease. Autoantibodies against other thyroid components as well as relative lymphocytosis supports the autoimmune basis of the disease. Both clinical and laboratory criteria for the diagnosis of Autoimmune thrombocytopenic purpura were also satisfied. In addition, the patient had some features of the acute type of autoimmune thrombocytopenic purpura, as defined by Hirsch and Dameshek (27).

There appears to be an increased prevalence of hyperthyroidism, and indeed of latent Graves' disease, in patients with autoimmune thrombocytopenic purpura (AITP). Marshall et al in 1967 estimated an incidence of 14% in his series of 42 patients with ITP (15). Evans and Perry found 4 cases of thyrotoxicosis in his review of 75 cases of thrombocytopenia (9). However, a more recent study of 275 patients with ITP by a Thai group from 1960-1972 revealed an incidence of only 2.55% (19). This contrasts with prevalence of 1.9% in females and 0.2% in males, of thyrotoxicosis, in the general population.

Woodruff, in contrast, found platelet numbers to be significantly lower in thyrotoxic patients as compared with normal adults (8). Kurata in 1980 produced evidence showing that 43% of patients with untreated hyperthyroidism had platelet counts less than 150,000/mm^3 (28). It therefore seems that thrombocytopenia is likely to occur in severely hyperthyroid patients but the prognosis being usually good owing to the fact that megakaryocytes are present in the bone marrow. Past series have shown that there are normal or increased number of megakaryocytes in the bone marrow in hyperthyroidism, independent of the number of circulating platelets (17, 29, 30).

This patient is the 4th girl of Chinese extract to be described. The first 3 were part of a 1975 Thai series. As the Chinese were a minority in Thailand, attention was called to whether there was a preponderance of this association in the Chinese race.

Two recent studies have reported female to male ratio of thyrotoxicosis associated with thrombocytopenia as 3.1 to 1 and 6 to 1 respectively (19, 22). This compares to the sex ratio of 7 females to 1 male for thyrotoxicosis in non-endemic areas (31).

The average age of patients with this association was

found to be 43 years, the range being from 0 to 72 years (22). Thyrotoxicosis usually affects those in the first 3 decades of life while there is a biphasic age distribution for autoimmune thrombocytopenic purpura (young children being affected in the acute type while the 20 to 40 years age group is affected for the chronic type).

The clinical features present in this patient was also analysed in Herman's series. He found that 75% had a diffuse goitre, an unpalpable spleen in 58% and lymphocytosis in 22% (22). Adrouny et al, in 1982, described 5 cases with variable clinical presentation and response to treatment (26). He believed the underlying mechamism to be due to the overlap of the 2 'major' theories.

The first major theory relates thrombocytopenia as a secondary effect of the thyrotoxic state. Lamberg et al described shortened platelet survival in 6 patients with hyperthyroidism and demonstrated a shortened life span using 51Cr labelling. He attributed this decrease in platelet survival to be due to slight hypersplenism occurring in hyperthyroidism (17). Kurata, with rat and human studies, supported this view and suggested that the thrombocytopenia in Graves' disease was due to the increased sequestration of platelets by an activated reticulo-endothelial system in the hyperthyroid state. It was concluded that the thrombocytopenia in Graves' disease was closely related to the level of thyroid function but was independent of the underlying cause of thyrotoxicosis (28).

A large number of the recent authors, however, tend to favour the opposing theory — that which attributes the basis of the condition to autoimmunity. Marshall et al in 1967 were probably the first to speculate that both diseases were related by virtue of autoimmunity and he suggested that the etiologic agent in immune thrombocytopenic purpura may be similar to so-called long acting thyroid stimulator (LATS) (17). In 1971, Dunlap et al demonstrated the presence of IgG markers specific for both Graves' disease and immune thrombocytopenic purpura in a patient, confirming the presence of 2 diseases — this concurrence suggesting an underlying relationship. He further demonstrated a dissociation between thyroxine concentration and platelet counts as evidenced by the poor temporal relationship between platelet counts and thyroxine levels and therefore concluded that this was an indication of the presence of 2 independent processes rather than the concept that immune thrombocytopenic purpura was a consequence of hyperthyroidism (18). Herman et al described a patient whose serum thromboagglutinins became negative after subtotal thyroidectomy thereby underlining a. possible autoimmune relation. In Hymes' 1981 study, elevated platelet bound IgG levels were demonstrated in 50% of patients with Graves' disease. He speculated that this IgG may be an antiplatelet antibody within the family of autoantibodies in the Graves' — Hashimoto's diathesis (32).

Branehog et al, described 2 patients in which thyrotoxicosis was associated with immune thrombocytopenic purpura, as well as hemolytic anaemia. In these cases, it was proved that the thyrotoxicosis was due to lymphoid thyroiditis and the severe thrombocytopenia due to very short platelet survival. It was speculated that there was a common mechanism involving an antibody dependent, cell mediated immunity directed against red blood cells, platelets and thyroid tissue. It was also suggested that despite the great array of antibodies present, the basic abnormality was confined to immunocompetent T-lymphocytes (24). In addition, thrombocytopenia and autoimmune diseases such as Myasthenia Gravis have been described in association with Hashimoto's disease (33, 34) as well as Graves' disease (35).

The authors believe that both autoimmunity and the reticuloendothelial system play interlinked roles in the association of Graves' disease and thrombocytopenia. The basic defect is probably a genetic abnormality in immune surveillance which may permit a particular clone of lymphocytes to survive, proliferate and secrete the stimulatory immunoglobulins in response to certain precipitating factors. These immunoglobulins are of the IgG type and act against various tissues — among which are platelets and the thyroid. It is possible that the antiplatelet antibody and the so-called TSI (thyroid stimulatory immunoglobulin) are the same immunoglobulin. This immunoglobulin or its thyroid stimulatory and/or antiplatelet part will then act along the path shown in the diagram. The final common pathway is likely to be through the reticuloendothelial system in which there is increased sequestration of platelets, resulting in decreased number of platelets peripherally. The clinical pattern of the disease and its response to treatment is probably dependent on whether the 'thyroid stimulating' or the 'antiplatelet' "ability" of the immunoglobulin is predominant. This property is probably determined genetically.

The mode of treatment in this disease has not been well established. In Herman's series, platelet counts returned to normal levels after patients were rendered euthyroid in 82% of the cases (22). There have been isolated reports describing therapy but Adrouny et al (1982) was the first to classify the 4 clinical patterns of the disease, namely: (1) Thrombocytopenia which resembled idiopathic thrombocytopenic purpura and responded to prednisolone therapy, (2) Thrombocytopenia which remitted with treatment of the thyrotoxicosis, (3) Remission of thrombocytopenia occurring despite persistent hyperthyroidism, (4) Thrombocytopenia which persisted despite correction of the hyperthyroidism (26). It has been suggested that the mild and more common type of thrombocytopenia (platelet counts more than 50,000/mm^3) may have thyrotoxicosis induced reticuloendothelial activation as a predominant mechanism. These were unlikely to bleed significantly and it was suggested that these patients be treated only for thyrotoxicosis (19, 26, 30). It was concluded that patients with more severe thrombocytopenia be given additional treatment especially if there is overt or potential bleeding (26).

Evaluation of thyroid function is indicated in every patient with unexplained thrombocytopenia or thrombocytopenia refractory to the usual treatment. Subclinical thyrotoxicosis may then be detected. In view of the potential myelotoxicity of antithyroid drugs, all thyrotoxic patients should undergo a complete blood count before therapy is started (22, 23).

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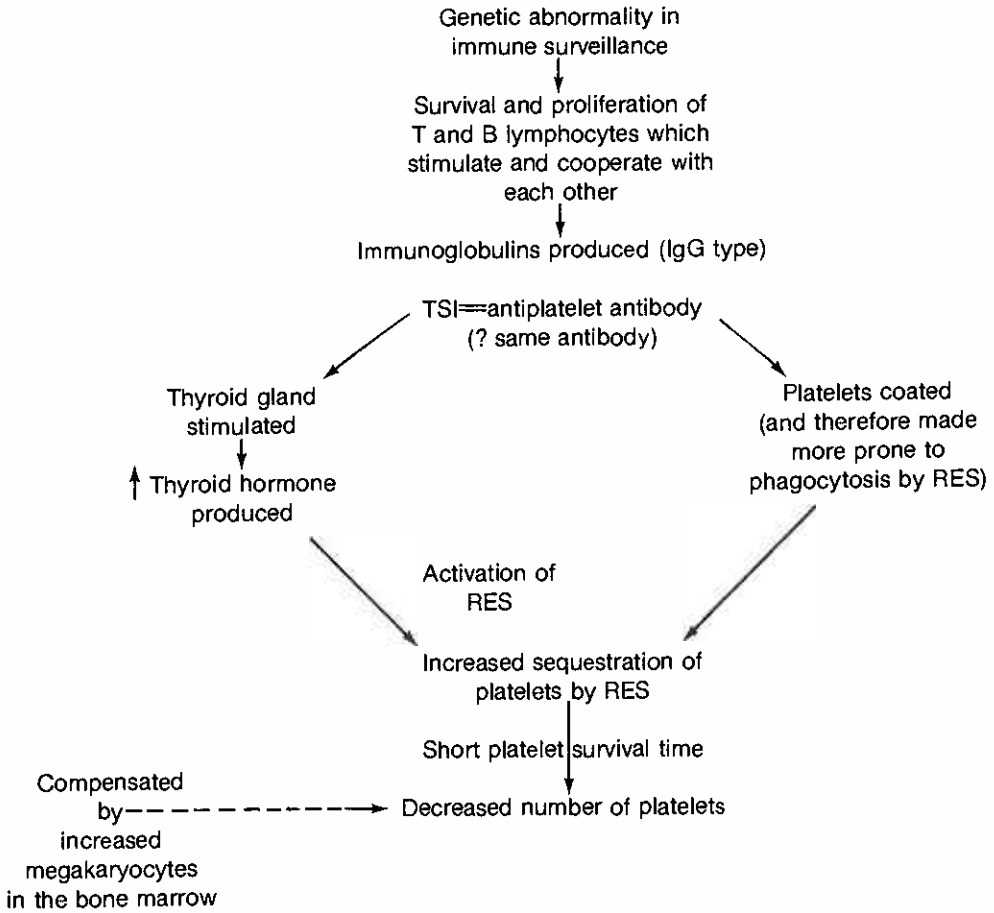
DIAGRAM:

POSTULATED MECHANISM OF THE THROMBOCYTOPENIA-GRAVES' DISEASE ASSOCIATION



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