Acquired von Willebrand's disease and hypothyroidism: report of a case presenting with menorrhagia

N.E. Blesing, H. Hambley and G.A. McDonald

Department of Haematology, Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK.

Summary: A 17 year old woman presented with severe anaemia due to menorrhagia. On investigation, she was shown to have abnormalities of her haemostatic mechanism consistent with von Willebrand's disease Type I, although there was no family history of this disorder. In addition, she was shown to have severe primary hypothyroidism. On correction of hypothyroidism with oral thyroxine, her coagulation defects returned to normal and menorrhagia ceased. This is consistent with acquired von Willebrand's disease secondary to hypothyroidism.

Introduction

Menorrhagia and easy bruising are stated to be commonly occurring presenting symptoms in hypothyroidism.^{1,2} Anaemia is found not infrequently in patients with hypothyroidism: in a review of 202 cases, 23% of female patients and 47% of male patients were found to be anaemic at presentation.³ Despite this, significant blood loss in patients with untreated hypothyroidism has been reported only rarely.^{4,5} A possible link between the two could be a haemostatic defect similar to that of von Willebrand's disease which would be present in the untreated state and which would resolve on effective therapy of the hypothyroidism, i.e. acquired von Willebrand's disease.⁶

Case report

The patient was a 17 year old female who had been well until 10 days previously when she started to menstruate. After 3 days, the blood flow increased and she started to complain of tiredness. She consulted her general practitioner who requested a full blood count which was reported as showing pancytopenia with atypical cells, possibly blasts, seen on the peripheral blood film.

She was referred to the Haematology Department of Glasgow Royal Infirmary for further investigation. On admission, she complained of tiredness and continued to have vaginal blood loss. Although her menstrual cycle was irregular, she had not had menorrhagia in the past. She denied

any history of easy bruising, of epistaxis or of excessive blood loss following surgical or dental procedures. There was no family history of a bleeding disorder nor of any thyroid disorder. Apart from oral ferrous sulphate which had been started by her general practitioner at the initial consultation, she was not taking any other medication.

On examination, she was anaemic. Height was 145 cm and weight was 61 kg. There was no lymphadenopathy nor splenomegaly. Examination of the cardio-respiratory and gastrointestinal system was normal. Apart from some puffiness of her face, there were no other features suggestive of a thyroid disorder. Gynaecological examination was normal.

Investigation of peripheral blood revealed haemoglobin concentration of 52 g/l, total leucocyte count of $8.5 \times 10^9/l$ and platelet count of $263 \times 10^9/l$. Reticulocyte count was elevated at 9% and mean red cell volume (MCV) was elevated at 100 fl (the normal range for this laboratory, 76–96 fl). Peripheral blood film showed polychromasia of erythrocytes with an occasional nucleated red cell being seen; leucocytes were normal in type and distribution and, in particular, no blast cells were seen. Bone marrow aspiration yielded only blood. However, trephine biopsy showed a marrow of slightly decreased cellularity but with normal maturation of all cellular elements. Results of investigation of haemostatic system are shown in Table I.

Renal and liver function tests were normal. Thyroid function tests were as follows: serum thyroxine (T₄) 26 nmol/l (normal range 55–144 nmol/l), serum tri-iodothyronine (T₃) 0.8 nmol/l (normal range 0.9–2.8 nmol/l) and

Table I Results of haemostatic investigation before (Pre Rx with T4) starting therapy with thyroxine and after restoration of euthyroid state (Post Rx with T4)

	Pre Rx with T4	Post Rx with T4
One stage prothrombin time (normal range 12–15 seconds)	15	15
Kaolin cephalin clotting time (normal range 36–50 seconds)	42	43
Thrombin clotting time (normal range 6–9 seconds)	8	6
Factor VIII:C (normal range 50–190 IU/dl)	36	120
von Willebrand factor antigen (normal range 50–146 IU/dl)	36	79
Ristocetin cofactor (normal range 50–172 IU/dl)	31	71
von Willebrand factor multimers	normal	normal
Bleeding time (normal range 3–9 min)	11.5	7

serum thyroid stimulating hormone (TSH) 272 mU/l (normal range < 5 mU/l). Thyroid microsomal antibody and thyroglobulin antibody were negative.

Initial therapy included blood transfusion to correct anaemia and oral thyroxine, initially 50 µg daily and gradually increasing to 200 µg daily to correct hypothyroidism. On this therapy, she became euthyroid and menstruation became regular with no recurrence of menorrhagia. Haemostatic function (Table I) has returned to normal and the haemoglobin has remained stable without any blood transfusions or haemotonic therapy.

Materials and methods

Full blood count was performed using Coulter S Plus (Coulter Electronics Ltd, Bedford). Coagulation studies were performed manually using standard methods.⁷ Factor VIII:C was measured by a One-stage technique.⁸ Von Willebrand factor antigen (vWF:Ag) was assayed by a Laurell technique⁹ and Ristocetin Co-factor (RiCoF) was measured by a platelet aggregation method.¹⁰ Analysis of multimers of von Willebrand factor (vWF) was performed by SDS polyacrylamide gel electrophoresis.^{11,12} Bleeding time was measured by

a template method (Simplate, General Diagnostics, New Jersey, USA).

Discussion

The patient described above showed defects in her haemostatic system consistent with the diagnosis of von Willebrand's disease, type IA. The main clinical effect of this was menorrhagia which caused severe anaemia requiring blood transfusion. The patient was found to be severely hypothyroid and on correction of the hypothyroid state, the haemostatic defects returned to normal suggesting that the lack of thyroid hormones played a fundamental role in the decreased levels of factor VIII which on multimeric analysis was normal, i.e. there was a quantitative rather than a qualitative defect of factor VIII production.

Acquired von Willebrand's disease has been associated usually with a circulating IgG antibody which acts as a functional inhibitor of the factor VIII molecule and which has been associated with various underlying disorders such as systemic lupus erythematosus,^{13,14} non-Hodgkin's lymphoma¹⁵ and myeloma.¹⁶ However, recent reports have indicated that hypothyroidism may cause a decrease in the circulating factor VIII level without the presence of an inhibitor.^{6,17} The precise mechanism is not known; at a cellular level triiodothyronine acts on nuclear receptors to cause an increase in m-RNA sequences¹⁸ and it is tempting to speculate that, in the presence of reduced levels of thyroid hormone, decreased amounts of m-RNA specific for factor VIII components would lead to a decrease of the synthesis of the factor VIII molecule. The possibility of acquired von Willebrand's disease and hypothyroidism should be kept in mind in patients presenting with menorrhagia. Unexplained bleeding or easy bruising in patients presenting with hypothyroidism should prompt full investigation of the haemostatic system.

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