A bleeding disorder due to deficiency of α_2 -antiplasmin

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SUMMARY The investigation of a 33 year old man with a lifelong bleeding tendency is described. Defective fibrinolysis was suspected in 1968, when clinical bleeding was corrected by administration of aminocaproic acid. The paper establishes the diagnosis as α_2 -antiplasmin deficiency and describes its management with oral tranexamic acid.

α_2 -Antiplasmin is a plasma proteinase inhibitor with an estimated molecular weight of 65 000–70 000 daltons. It is a potent inhibitor of plasmin, its covalent binding to fibrin being mediated by factor XIIIa. Bound to fibrin, α_2 -antiplasmin reduces plasmin mediated fibrinolysis. Inherited lack of α_2 -antiplasmin leads to increased fibrinolysis and a haemorrhagic diathesis. There are reports of congenital α_2 -antiplasmin deficiency in Japan,¹ Holland,² and the USA.³ This paper documents a further case of congenital α_2 -antiplasmin deficiency, the first description of the condition in a United Kingdom citizen.

Material and methods

Routine coagulation tests were performed by standard methods. Euglobulin clot lysis time was measured on a Malin Electronics clot lysis time recorder by the method of Nilsson and Olow.⁴ Plasminogen estimation was carried out by a caseinolytic assay.⁵ The electroimmunoassay method of Laurell⁶ was used to measure: α_2 -antiplasmin, α_2 -macroglobulin, antithrombin III, and antitrypsin. Antiserum against α_2 -antiplasmin was supplied by Seward Laboratories Limited; others came from Behring Diagnostics. Total antiplasmin was measured chromogenically using Kabi substrate S2251, employing the manufacturer's method. Antithrombin III (functional) was determined chromogenically using Kabi S2238 substrate. Results are expressed as a percentage of the ranges established in normal donor plasma samples.

CASE HISTORY

The propositus is a 33 year old man; his parents

were second cousins but no relative has a bleeding disorder. The patient gave a history of spontaneous bruising since the age of 3, frequent epistaxes, and was admitted to hospital aged 7 because of excessive bleeding after a thumb laceration. Thereafter, he had excessive bleeding following dental extraction, and at the age of 17 he was readmitted to hospital for uncontrollable bleeding after dental surgery. In 1968 he underwent planned surgical removal of disfiguring supra- and infrapatellar cysts, which originated from slow resolving post-traumatic haematomata. He bled profusely, and bleeding restarted 8 h after initial haemostasis. Administration of intravenous aminocaproic acid controlled the bleeding and successful healing ensued.

Subsequently, oral tranexamic acid has controlled any bleeding episode. He has not suffered from spontaneous haemarthroses and bleeding episodes have become less frequent with increasing age.

Investigations and laboratory findings

Multiple investigations were performed over the years in an attempt to delineate his bleeding diathesis. There was no evidence of underlying liver or collagen disease. The excised surgical material consisted of simple synovial cysts with accompanying fibrosis.

Detailed coagulation studies were performed between 1958 and 1984, and there was no coagulation factor deficiency, acquired circulating anticoagulant, or platelet abnormality. During his admission in 1968, however, minimal evidence of defective fibrinolysis was obtained. Before operation a shortened euglobulin clot lysis time of 60 min and an increased concentration of fibrinogen/fibrin degradation products of 160 $\mu\text{g/ml}$ was found.⁷ The cysts had enlarged clinically before admission, which suggests the occurrence of occult haemorrhage

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Plasma proteinase inhibitor values

Test	Immunological		Functional	
	Patient	Sister	Patient	Sister
α_2 -Macroglobulin	102%	62%	—	—
α_2 -Antitrypsin	115%	98%	114%	93%
Antithrombin III	120%	96%	150%	93%
Total antiplasmin	—	—	15%	140%
α_2 -Antiplasmin	None detected	82%	—	—

Results are expressed as a percentage of the ranges established in normal donor plasma samples (range 70–110%).

within the cysts. Eight hours after operation severe haemorrhage occurred and treatment with intravenous aminocaproic acid was instituted: 8 g as a stat dose followed by 1 g hourly. Rapid haemostasis was achieved within the hour. Twelve hours later the fibrinogen/fibrin degradation products had risen to 1288 $\mu\text{g/ml}$,⁷ the plasminogen had fallen from 2.8 to 1.2 casein units, and the euglobulin clot lysis time showed a firm clot at 120 min. Thereafter, fibrinolytic studies carried out as an outpatient were normal. In 1984 his α_2 -antiplasmin concentration was estimated (Table) and the diagnosis of α_2 -antiplasmin deficiency was established.

Discussion

Previous reports of congenital α_2 -antiplasmin deficiency suggest an autosomal recessive form of inheritance. The present case shows a history of consanguinity as in the original case report.¹ The patient's parents are dead and only one sibling was available for study. Her results were normal (Table).

The present case differs from those reported previously in that the bleeding diathesis is less severe. But the total antiplasmin activity is thought to reflect the other plasma proteinase inhibitors, especially α_2 -macroglobulin. Our patient's residual activity (15%), being higher than that reported by Klufft (2%), may explain the decreased severity of his bleeding. His pattern of rebleeding 8–12 h after achieving initial haemostasis is typical, suggesting that clots are formed normally but are rapidly lysed because of lack of inhibition of fibrinolysis. These

results are similar to those described by Klufft² and emphasise that present routine methods of testing fibrinolysis may be inadequate. α_2 -Antiplasmin deficiency should therefore be considered in any unexplained bleeding diathesis. Furthermore, treatment is readily available in the form of tranexamic acid.

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