Acquired Haemophilia – A Therapeutic Challenge

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Summary

Acquired haemophilia is a rare clinical condition arising from the spontaneous development of inhibitors to factor VIII. We describe two cases encountered in the University Hospital over the past five years. We also review the literature and discuss the therapeutic difficulties faced in dealing with patients with high levels of inhibitors. In one of these patients we also describe, for the first time in this region, a novel method in managing the acute bleeding episode in acquired haemophilia using recombinant factor VIIa.

Key Words: Acquired haemophilia, Factor VIII inhibitor, Recombinant factor VIIa

Introduction

The development of antibodies to factor VIII is a well-recognised phenomenon and occurs in about 15% of haemophilia patients. What is far less common is the spontaneous development of antibodies to factor VIII in individuals without haemophilia.

Approximately 87% of patients with this disorder experience serious bleeding and in 22%, mortality can be attributed to the presence of the inhibitor[1].

The seriousness of this disorder is exacerbated when high levels of inhibitor are encountered. Patients with high levels of inhibitor are not likely to undergo spontaneous remission of their illness. In treated patients in whom the inhibitor persists, the mortality is as high as 40%. Moreover, the therapeutic options are limited in patients with high levels of inhibitor to factor VIII, as transfusions of factor VIII concentrate or cryoprecipitate are rendered ineffective by the antibody.

We describe two patients who spontaneously developed high levels of inhibitors to factor VIII and presented to us with major bleeding. We also describe the usage, for the first time in this region, recombinant factor VIIa to arrest the severe bleeding episode in this disorder in one of these patients. We also review the literature for reports of acquired factor VIII inhibitor and summarise the findings.

Method and Materials

Coagulation assay

Blood (4.5 mls) was withdrawn from a clean venepuncture using plastic syringes and collected in vacutainer tubes (Becton Dickinson) containing 0.5 mls of 0.129 M trisodium citrate. The blood was centrifuged for 10 minutes at 3000 rpm at 18°C in a refrigerated centrifuge. All coagulation tests, except thrombin time, were performed on the ACL 200

(Automated Coagulation Laboratory 200, IL (Coulter Electronic (Hongkong) Ltd. Prothrombin times were assayed using Thromboel S (Behring, Hoechst Malaysia Sdn Bhd). Fibrinogen levels were derived from the delta light scatter at equilibrium of the prothrombin time reaction curve. Topical Thrombin, (Bovine origin from Parke Davis) diluted with saline was used for the preparation of thrombin solution. This was adjusted with pooled normal plasma to give a clotting time of 16-19 seconds for thrombin time estimation. IL test APTT Micronized Silica (Instrument Laboratory) was used for all activated partial thromboplastin times as well as for the determination of Factor VIII:C. Factor VIII:C was estimated by the one stage APTT technique using Stago Unicalibrator as reference plasma and Factor VIII deficient plasma from Behring. Inhibitor screening tests were performed by mixing equal volumes of normal plasma with patient plasma. APTTs were performed on the freshly mixed plasmas and the mixed plasmas that were incubated at 37 C for one hour and also at two hours. The times were compared with the APTTs of normal plasma and patient's plasma that were incubated concomitantly. This is to determine whether the inhibitor was immediate acting or time dependent. The Factor VIII inhibitor was quantitated by the Bethesda method[2].

Literature search

A Medline (on CD Rom) search of the English language literature was made over a 15 year period from 1977 to 1992. All case reports of acquired factor VIII inhibitor or acquired haemophilia were noted and the findings summarised.

Case report

Case 1

The patient, a 37-year-old housewife, presented with spontaneous bruising over the limbs for four days associated with menorrhagia and slight pain in the neck aggravated by swallowing. She also complained of severe abdominal pain for one day prior to admission. Physical examination revealed multiple bruises on the limbs and a haematoma in the neck. The abdomen was tender and guarded in the lower quadrants but bowel sounds were preserved. An ultrasound of the pelvis showed free fluid, consistent with blood in the pelvic cavity. She gave a history of idiopathic thrombocytopaenic purpura (ITP) 12 years prior to this admission. She underwent a splenectomy a year following the diagnosis of ITP. Since the splenectomy she did not require oral steroids. She developed bronchial asthma 3 years prior to admission and had been treated with metered dose inhalers. There was no other significant drug history nor any family history of bleeding disorder. She has four children and the last pregnancy was 2 years prior to this illness. A full blood count done on admission was: Haemoglobin 112 g/l, Platelets 740X10^9/l and White cell count 15.1x10^9/l. Bleeding time was normal (1.7 minutes). Prothrombin time ratio was 1.0. The APTT was prolonged to 91.3 s. An inhibitor to Factor VIII was demonstrated by incubating the patient's plasma with normal plasma. The Factor VIII coagulant activity was markedly reduced to only 2%. The level of inhibitor obtained was extremely high, being 61.5 Bethesda units. A screen for systemic lupus erythematosus was negative. The complement levels were: C3 78 mg/dl and C4 18 mg/dl. DNA Ab was negative and the ANA was positive only in low titre (1:40).

She initially received 15 units of cryoprecipitate which did not have any clinical effect. Treatment with recombinant factor VIIa (rFVIIa, Novo Nordisk) was subsequently commenced at a dose of 90µg/kg intravenously every 2 hours. The abdominal pain and the neck haematoma subsided and no further bleeding was noted within two days of commencement of rFVIIa. The frequency of administration of rFVIIa was reduced to 3 to 4 hourly intervals and the drug was ceased after one week. At the same time, cyclophosphamide and prednisolone were commenced in an effort to reduce the level of inhibitor production.

The patient remained well until 5 weeks after diagnosis when she presented with a small sublingual bleed which subsided with a short course of tranexamic acid. The APTT at that time was 96.7s. At seven months follow-up the APTT was 84s. Despite the persistent prolongation of the APTT she did not have any further episodes of bleeding up and remains on low dose prednisolone together with pulse intravenous cyclophosphamide in an effort to further reduce the inhibitor levels.

Case 2

The second patient is a 25-year-old nulliparous, single Chinese woman from Sarawak who presented with one week of bruising in the limbs and one day's history of severe left sided loin pain associated with gross haematuria and vomiting. Physical examination revealed bruising in the upper limbs and marked tenderness in the left lumbar region. Haematuria was confirmed on urine microscopy. There was no previous nor family history of bleeding tendencies and she was not on any medication of note. The blood count was Hb 93 g/l, Platelets $203x10^9$/l, White cell count $9.9x10^9$/l. The renal function was normal and an ultrasound of the kidneys and an IVU showed mild left hydronephrosis with a suggestion of a blood clot in the upper pole of the left kidney. The Prothrombin time ratio was 1.0 and the APTT was 57.9s. The bleeding time was 1.4 minutes. Factor VIII inhibitor was demonstrated by incubating the patient's plasma with normal plasma. The factor VIII coagulant activity was 6.5% and the inhibitor level was 39.2 Bethesda units.

Initial treatment with Factor VIII concentrate totalling 2000 units did not elicit any rise in the Factor VIII level. Treatment with Factor IX concentrate was then commenced. The haematuria stopped and the abdominal pain subsided markedly after two days of Factor IX administration. She was simultaneously commenced on cyclophosphamide and prednisolone. Two weeks after admission she remained well without any evidence of further bleeding although the APTT was still high at 55.8s. She requested discharge to return to her home state in East Malaysia and has since been lost to follow-up.

Results

There were 65 cases of acquired factor VIII inhibitor reported in the English language literature from 1977 to 1992. Table I summarises the underlying diseases associated with the development of factor VIII inhibitors in these patients. The distribution of underlying diseases is very similar to that noted in the survey by Green and Lechner[1]. The majority of patients were adults with the exception of two reported cases occurring in childhood. Treatment was initiated in 50 (77%), the majority employing some form of immunosuppressive therapy, invariably incorporating steroids.

Discussion

The two cases reported typify the clinical presentation of acquired haemophilia A – adult onset, isolated prolongation of the APTT, presence of an identifiable inhibitor to factor VIII, low factor VIII coagulant activity and serious bleeding not correctable by infusions of factor VIII. The absence of an underlying

Table I
Underlying causes of acquired factor VIII inhibitor

Underlying Disease	Number (Percentage)
Nil	29 (44.6)
Solid tumours (carcinomas)	9 (13.8)
ca. bronchus	2
ca. prostate	2
ca. colon	1
ca. kidney	1
ca. epiglottis	1
ca. biliary tract	1
ca. pancreas	1
Post-partum	8 (12.3)
Autoimmune diseases	6 (9.2)
rheumatoid arthritis	4
systemic lupus	1
polyarteritis nodosa	1
Haematological diseases	5 (7.7)
hairy cell leukaemia	1
acute myeloid leukaemia	1
myelodysplastic syndrome	1
Hodgkin's lymphoma	1
mycosis fungoides	1
Miscellaneous[a]	5 (7.7)
Drugs[b]	3 (4.6)

a – leprosy, diabetes mellitus, lung abscess, multiple sclerosis, hereditary haemorrhagic telangiectasia
b – methyldopa, phenytoin, chlorpromazine

cause should not be a point against this diagnosis as at least 40% of patients do not have an underlying or associated disease.

The goals of treating of this condition should be firstly to arrest the bleeding episode and secondly to reduce the level of inhibitors to factor VIII. The level of inhibitor encountered determines the treatment modality aimed at stopping the bleeding. Patients with low levels of inhibitor (less than 10 Bethesda units) may not require treatment if the bleeding is clinically not troublesome and indeed in these patients, the disease may undergo spontaneous remission. Spontaneous remission may also occur in patients in the post-partum period. Conservative measures such as immobilisation, compression and on occasion administration of ε-aminocaproic acid or tranexamic acid may suffice for minor haemorrhages. For patients with low titre inhibitors, high dose factor VIII concentrates 50-100 ü/kg can be administered to control more serious bleeding. DDAVP has also been tried with success.

For patients with high levels of inhibitors, it is not practical to use factor VIII either in the form of concentrates or cryoprecipitate to treat bleeding episodes because the factor VIII will be rapidly neutralised once administered. Efforts are thus best directed at "bypassing" the site of inhibitor action. As the inhibitor is specific for human factor VIII and cross reacts poorly with that from other species, administration of porcine factor VIII has been tried. Disadvantages of porcine factor VIII therapy include the occasional severe allergic reaction and the possible loss of effectiveness with repeated infusions due to the development of anti-porcine inhibitors.

Alternatively, unactivated factor IX (in the form of prothrombin complex concentrate, PCC) or activated prothrombin complex concentrate (APCC) may be administered in an attempt to achieve haemostasis by "bypassing" factor VIII and activating the final common pathway of the coagulation cascade. However, PCC or APCC seems to be effective in only about 50% of bleeds. Moreover, thromboembolic complications have been reported[3].

Activated factor VII (FVIIa) is an attractive candidate as a factor VIII bypassing agent as it is not proteolytically active by itself and does not induce systemic activation of the coagulation cascade and therefore does not cause thromboembolic events. Factor VIIa requires the presence of tissue factor at the site of injury and the FVIIa-tissue factor complex induces local haemostasis with the formation of a local haemostatic plug. While plasma-derived factor VIIa has been purified, the difficulties in producing large quantities coupled with the inherent risk of transmitting blood-borne viruses precludes its wide spread use. Recombinant factor VIIa (rFVIIa, Novo Nordisk, Denmark) has been recently synthesised and used in at least 57 patients with inhibitors to factor VIII (both haemophiliac and non-haemophiliac). The chief constraints of this novel and highly effective method of treatment would be the need to administer the drug at frequent intervals (2-3 hours) in view of the short half-life, and also the cost of the recombinant product.

The second goal of treatment would be to reduce or to eliminate the inhibitor. This would be warranted when spontaneous disappearance of the inhibitor is not expected, as in the two cases described. Short term benefits may be derived from procedures utilised to remove the antibody from plasma, such as extracorporeal adsorption and exchange plasmapheresis.

Intravenous IgG has also been reported to be effective perhaps by an anti-idiotype effect on the inhibitor.

It would be justifiable to initiate immunosuppressive therapy for patients with persistent inhibitors. One would usually use steroids with or without a second agent such as cyclophosphamide or azathioprine. Overall, at least 58% of patients treated with immunosuppressive therapy will improve.

Future therapeutic prospects lie in the understanding of the mechanisms of this disease. Specific therapies that can block the ongoing immune response against autoantigens might be more efective. These approaches include antibodies that inhibit T-cell activation, peptides that block self-antigen binding and antibodies that inhibit MHC recognition.

References

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Osteogenesis Imperfecta and Non-accidental Injury: Problems in Diagnosis and Management

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Summary

It has been noted in the literature that Osteogenesis Imperfecta is frequently mistaken for non-accidental injury. This article serves to illustrate the difficulty in differentiating between the two conditions and that they can occur concomitantly in one patient.

Key Words: Osteogenesis Imperfecta, Non-accidental injury, Child abuse

Introduction

Non-accidental injury or child abuse is now reported frequently in many developed and developing countries. In most cases, the condition is very obvious both from the history and on physical examination of the children concerned. However, the clinician, in his evaluation of a suspected case of child abuse with fractures, must also consider concomitant medical conditions so as to organise a more comprehensive plan of action and thus avoid unnecessary separation of the child from his/her family. The most frequent of these conditions is Osteogenesis Imperfecta (OI), a hereditary condition occurring in about 1 out of 20,000 of the population[1,2]. Osteogenesis Imperfecta is a heterogenous group of disorders often brought to medical attention because of recurrent and multiple fractures, resulting from biochemical disorders of collagen or collagen production. Sillence, Senn and Danks[1] from their experience of 155 patients in