

A child with acquired haemophilia

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Introduction

Acquired haemophilia A (AHA) is a rare bleeding disorder with high morbidity and mortality due to development of autoantibodies against coagulation factor VIII (FVIII). AHA is frequently seen in elderly and the incidence is approximately 1 case/ million/ year [1]. The incidence in children under age 16 is 0.045/ million/ year [1]. It is associated with autoimmune disorders, malignancies, drugs, infections and pregnancy. However 50% of the AHA cases have no such association [2, 3].

Case report

A 14-year old boy with a history of developmental delay presented with sudden onset pain and swelling of his right thigh. He had no fever or history of trauma to the leg. His clinical examination revealed pallor and significant pain and swelling of the right thigh which was expanding. There was no redness or warmth over the area suggestive of inflammation process. The ultrasound scan revealed an intramuscular haematoma within the anterior thigh muscles. His past and family history were negative for bleeding disorders. He had no transfusion history of blood or blood products. While in the ward he developed large subcutaneous bleeds over right forearm, left arm and posterior aspect of left thigh (Figure 1).

His hemoglobin was 8.4g/dl. The platelet count (248,000/ μ l) and bleeding time (2 min) were normal with an isolated prolongation (76 s) of activated thromboplastin time (APTT). Prothrombin time (PT-12 s) and thrombin time (TT-19 s) were normal. Mixing studies with normal plasma showed an immediate correction of APTT (36 s) but 2 hour incubation could not correct APTT (54 s) indicating the presence of a time and temperature dependent inhibitor against clotting factors. Factor assay showed a very low factor VIII level of 0.1%. Factor inhibitor level was 21 Bethesda units (by Nijmegen modification). A diagnosis of acquired haemophilia A due to factor VIII inhibitor was made. He was negative for antinuclear antibody test (ANA), hepatitis B and hepatitis C serology. Contrast CT scan of abdomen and thorax was normal. Initially patient was treated with fresh frozen plasma (FFP)

and cryoprecipitate with no significant response. Once the diagnosis of AHA was confirmed, he was given prothrombin complex concentrates (PCC) 25u/ kg daily until bleeding settled. Three units of red cell concentrate were transfused. Immunosuppressive therapy with oral prednisolone 1mg/ kg daily started to eradicate auto-antibodies. After three weeks of prednisolone therapy, APTT remained prolonged (76 s). Therefore oral cyclophosphamide 2 mg/ kg/ day was added to the immunosuppressive therapy. After 5 weeks of therapy with prednisolone and cyclophosphamide, his APTT remained prolonged (68 s) and he developed two subcutaneous bleeding episodes. Then a decision was taken to treat him with PCC when he develops bleeding. We could not detect any concomitant disease causing AHA.



Figure 1. Large subcutaneous bleed over left posterior thigh.

Discussion

AHA is a rare bleeding disorder, first described in 1940 [4]. It is caused by autoantibodies directed against coagulation FVIII and associated with increased morbidity and mortality as severe bleeds can occur up to 90% of the

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patients [3]. The mortality rate is 8-22% with most deaths occurring in the first few weeks after presentation [4, 5]. These autoantibodies are usually of polyclonal IgG₁ and IgG₄ subclasses, leading to neutralization and/or accelerated clearance of FVIII from plasma in non-hemophilic persons [1, 2, 5]. The age distribution of AHA is biphasic with a small peak between 20-30 years due to postpartum FVIII antibodies and the major peak in patients aged 68-80 years [3]. More than 80% AHA patients are older than 65 years [1]. It is commonly associated with postpartum period, autoimmune diseases, underlying haematologic or solid cancers, infections (acute hepatitis B and C), or use of medications such as penicillin, chloramphenicol and phenytoin [1, 3]. In 50% of the cases no such relevant coexisting condition is found [1-4]. There are few reported cases of childhood AHA associated with solid tumours and insulin dependent diabetes [6].

The bleeding pattern of AHA is different from that of inherited haemophilia A, where haemarthroses being the commonest presentation. Most patients with AHA have haemorrhages into the skin, muscles or soft tissues, and mucous membranes (epistaxis, gastrointestinal and urologic bleeds), retroperitoneal haematomas or postpartum bleeding [1]. Haemarthroses are uncommon in AHA [1, 3].

The diagnosis of AHA is by demonstration of isolated prolongation of APTT which fails to correct on incubation of equal volumes of patients' and normal plasma at 37°C for 2 hours (mixing studies) [1-3]. Subsequent identification of reduced FVIII level and presence of FVIII inhibitors (by Bethesda assay or the Nijmegen modification) confirm the diagnosis [1, 3].

The treatment of AHA include control of acute bleeding episodes and long term eradication of the FVIII auto antibodies [1-3]. Antibody eradication requires treatment of any underlying condition [2]. Control of acute bleeding requires temporary restoration of the clotting cascade. Fresh frozen plasma (FFP) is not effective because it contains only a small amount of FVIII which will be rapidly inactivated by circulating antibodies especially if the antibody titre is very high. Similarly the response to human FVIII concentrates is inadequate unless inhibitor level is very low (< 5BU) [3]. Desmopressin (DDAVP) alone or in combination with human FVIII concentrates may be effective when treating minor bleeds with low inhibitor levels [3, 4]. Factor VIII inhibitor bypassing agents are currently the most effective and widely used treatment for controlling acute bleeds. Bypassing agents include

recombinant activated factor VII (rFVIIa, 90-120 µg/ kg/ 2-3 hourly) and activated prothrombin complex concentrate (aPCC, 50-100 IU/ kg / 8-12 hourly) and both agents have equal rates (93%) of bleeding control [1, 3, 4]. Similarly, both of these agents carry a thromboembolic risk which is higher in older AHA patient due to age related cardiovascular risk factors [1, 4]. Our patient was treated with PCC since aPCC was not available in Sri Lanka.

Patients with AHA should be immediately started on immunosuppressive therapy upon the diagnosis to eradicate autoantibodies [1, 2]. Common therapeutic options include corticosteroids alone or in combination with cytotoxic drugs (cyclophosphamide, azathioprine, 6-mercaptopurine and vincristine), rituximab, cyclosporine-A, intravenous immunoglobulin (IVIG), and immune tolerance induction [1, 3]. Treatment with corticosteroids (prednisolone 1-2 mg/ kg/ d) alone or in combination with cyclophosphamide (1.5-2 mg/ kg/ d) for 5 weeks, achieves the highest inhibitor eradication rates (70-80%) and is preferred as the first line therapy [1, 3]. Patients who recover, need follow up with APTT for a minimum period of one year since AHA can relapse in 20% cases.

Though AHA is a very rare disease, especially in childhood it should be taken as a differential diagnosis provided the clinical presentation is suggestive (ecchymosis, intramuscular and mucosal bleeding) since failure to treat early may lead to adverse consequences.

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