Hemophilia A

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Introduction
Hemophilia A is an X-linked hereditary disorder caused by defective synthesis of factor VIII. The estimated incidence of hemophilia A is 1 in every 5,000 to 7,000 live male births and it is more common than other inherited clotting factor abnormalities. It occurs in all ethnic groups in all parts of the world. Hemophilia A and B are the only two hereditary clotting factor defects inherited in a sex-linked pattern; they are clinically indistinguishable, although recent data suggest that on the average, hemophilia B may be less severe than hemophilia A. In an individual patient, the disorders cannot be distinguished without specific assay for factor VIII or IX.

Case Report
Patient is a 40 year old male who came to the Outpatient Clinic of Internal Department with chief complaint of swelling and deformity of his knees (Figure 1) for 4 weeks. He had been experiencing hematoma on the knee joints since 8 years without any preceding trauma, that make him unable to walk appropriately. Patient also had been experiencing spontaneous bleeding eg. gum bleeding since he was 12 years old. The patient had received blood transfusion once in 2006 and plasma transfusion twice during his 3rd year in junior high school and 2nd year in senior high school. There was no other specific complaints.

On physical examination, the patient was fully alert with normal blood pressure, no signs of fever. Swelling and deformities were found in his knee joints. Other abnormalities seen were hematoma in his right elbow. Laboratory results on February 18, 2011 showed Hb 14.6 g/dl, leucocyte 6,260/mm3, platelet 261,000/mm3, Urinalysis: hematuria (+), erythrocyte 1-6/field, prothrombin time: 15.8” (12.80”) (ratio=1.23); INR: 1.19; aPTT: 48.8” (30.0”) (ratio=1.62); thrombin time: 12.3” (11.8”) (ratio=1.04), bleeding time: 1’30”; D-dimer 60 ng/ml, factor VIII 35.4 % (55-150), factor IX 592% (70-140). Liver function test and renal function test were within normal limits. Patient were advised to be hospitalized.

Examination on February 25, 2011 showed increased APTT and decreased factor VIII; prothrombin time:16.8” (13.80”) (ratio=1.20); INR: 1.31; aPTT:102” (32.0”) (ratio=3.18); thrombin time: 20.2” (12”) (ratio=1.68), D-dimer=175 ng/ml, factor VIII= 20 % (55-150), factor IX=68% (70-140).

Radiological examination of his right knee (Figure 2a) revealed sclerotic area in tibia and irregular joint surface at the femur area with narrowed joint space. His left knee (Figure 2b) revealed former fracture angulated to the posterior left distal femur without any dislocation or space joint narrowing. The conclusion were: bilateral osteoarthritis particularly the right knee and malunion in distal left femur.

Current working diagnosis were hemophilia A with haemarthrosis in elbow joint and hemophilic arthropathy in right ankle and bilateral knee joint. The patient was given 5 vials of factor VIII concentrate (1 vial = 250 unit). The dose calculation: [Desired Factor VIII level (%normal) x kg.bodyweight]/2 = (50% x 46)/2 = 1,150 unit/250unit = 4.6 vials ~ 5 vials. After 4 days, patient’s condition improved and discharged from hospital.

DISCUSSION
Hemophilia A is a heterogeneous disorder resulting from factor VIII gene defects that leads to absent or reduced circulating levels of functional factor VIII. The reduced activity can result from a decreased amount of factor VIII protein, the presence of a functionally abnormal protein, or a combination of both.
Hemophilia A is characterized by excessive bleeding into various tissues of the body, including soft-tissue hematomas and hemarthroses that lead to severe crippling hemarthropathy. Recurrent hemarthroses are characteristic of the disease. The disease has been broadly classified as mild, moderate, and severe, although overlap exists between these categories. The classification of the severity of hemophilia has been based on either clinical bleeding symptoms or on plasma procoagulant levels, which are the most widely used criteria. Persons with less than 1% normal factor (<0.01 IU/mL) are considered to have severe hemophilia. Persons with 1-5% normal factor (0.01-0.05 IU/mL) are considered to have moderately severe hemophilia. Persons with more than 5% but less than 40% normal factor (>0.05 to <0.40 IU/mL) are considered to have mild hemophilia. Clinical bleeding symptom criteria have been used because patients with FVIII or FIX levels of less than 1% occasionally have little or no spontaneous bleeding and appear to have clinically moderate or mild hemophilia. Severely affected patients (<1% factor VIII) frequently experience "spontaneous" bleeding without known trauma. Without effective treatment, recurrent hemarthroses resulted chronic hemophiliac arthropathy in young adulthood and are highly characteristic for the severe form of the disorder. Severely affected patients are subject to serious hemarthroses that may dissect through tissue planes, ultimately leading to compromise vital organs. Bleeding episodes are intermittent, and some patients do not bleed for weeks or months. Except for intracranial bleeding, sudden death because of hemorrhage is rare.

Moderately affected patients with hemophilia may have occasional hematomas. Hemarthroses, usually associated with a known trauma may also occur. These patients have 1-5% of normal factor VIII activity. Mildly affected hemophilia patients with 6-30% factor VIII levels have infrequent bleeding episodes.

Most carriers have approximately 50% factor VIII activity and experience no bleeding symptoms, even in surgical procedures. Carriers with factor VIII level less than 50%, as a result of imbalanced X chromosome inactivation, may experience excessive bleeding after trauma (e.g., childbirth or surgery). Measurement of factor VIII level is recommended in all carriers.

This is a case of Hemophilia A with the complication of haematuria, haemarthrosis of elbows joints and arthropathy of knees joint and right ankle joint. Many severely affected patients with hemophilia experience episodes of hematuria. The urine may be brown or red, depending upon the rate of bleeding. Most bleeding arises from the renal pelvis, usually from one kidney but occasionally from both.

Bleeding into joints accounts for approximately 75 percent of bleeding episodes in severely affected patients with hemophilia A. The normal synovium has few cells, but numerous capillaries beneath the synovial layer can be damaged by mechanical trauma associated with daily use. The joints most frequently involved, in decreasing order of frequency are knees, elbows, ankles, shoulders, wrists, and hips. Hinge joints are much more likely to be involved than are ball-and-socket joints. Hemarthroses are heralded by an aura of mild discomfort that, over a period of minutes to hours, becomes progressively painful. The joint usually swells, warm, and exhibits limited motion. Occasionally, the patient experiences a mild fever. Significant and sustained fever, however, suggests an infected joint. When joint bleeding does not respond to replacement therapy, one should suspect an inhibition of factor VIII or an infected joint. Bleeding into knee joint is more easily detected by physical findings than is bleeding into either elbow or shoulder. When bleeding stops, the blood resorbs, and the symptoms gradually subside over a period of several days. If hemarthroses are treated early and the joint is not chronically involved, pain usually subsides in 6 to 8 hours and disappears in 12 to 24 hours. However, repeated hemorrage into the joints eventually results in extensive destruction of articular cartilage, synovial hyperplasia, and other reactive changes in adjacent bone and tissues. Iron deposits from residual blood is a major factor in the pathogenesis of hemophilic arthropathy. Acute bleeding into a chronically affected joint may be difficult to distinguish from the pain of degenerative arthritis.

A major complication of repeated hemarthroses is joint deformity complicated by muscle atrophy and soft-tissue contractures (Figure 1). Figure 2a, 2b and 3a shows the various radiologic stages of progressive destruction of joint cartilage and adjacent bone.

Rational treatment for hemophilia is to normalize the FVIII concentration. Various FVIII concentrates are now available. Reduced infectious complications and improved purity are the main advantages of these concentrates. Cryoprecipitate, one of blood product, can be given if F VIII concentrates is not available. A bag of cryoprecipitate contains 80-100 unit F VIII and can increase F VIII concentration by 35% but may cause allergic reactions and fever.

The dose requirement of FVIII concentrate can be calculated by formula based on the desired FVIII level (Table 2):

1. Plasma volume (PV) = 40ml/kg of bodyweight

FVIII concentrate (unit) = (PV x [(desired FVIII level (% of normal) x kg bodyweight)/2]

2. FVIII concentrate (unit) = (desired FVIII level (% of normal) x kg bodyweight)/2

CONCLUSION

FVIII concentrate injection of 1,150 unit (5 vials) has been administered to this Hemophilia A patient and will be given every 3 weeks. The medical rehabilitation were advised to overcome the deformities of hemophilic arthropathy.
Table 2. General guidelines for factor replacement for the treatment of bleeding in hemophilia.

<table>
<thead>
<tr>
<th>Site of Hemorrhage</th>
<th>Desired Factor VIII level (% of normal)</th>
<th>Factor VIII Dose (U/kg body weight)</th>
<th>Dose Frequency (every no. of hours)</th>
<th>Duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemarthroses</td>
<td>30–50</td>
<td>~ 25</td>
<td>12-24</td>
<td>1-2</td>
</tr>
<tr>
<td>Superficial intramuscular hematoma</td>
<td>30–50</td>
<td>~ 25</td>
<td>12-24</td>
<td>1-2</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>~ 50</td>
<td>~ 25</td>
<td>12</td>
<td>7-10</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>30-50</td>
<td>~ 25</td>
<td>12</td>
<td>Until resolved</td>
</tr>
<tr>
<td>Oral mucosa</td>
<td>30-50</td>
<td>~ 25</td>
<td>12</td>
<td>Until resolved</td>
</tr>
<tr>
<td>Hematuria</td>
<td>30-100</td>
<td>~ 25-50</td>
<td>12</td>
<td>Until resolved</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>50-100</td>
<td>50</td>
<td>12</td>
<td>At least 7-10 days</td>
</tr>
<tr>
<td>Retropharyngeal</td>
<td>50-100</td>
<td>50</td>
<td>12</td>
<td>At least 7-10 days</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>50-100</td>
<td>50</td>
<td>12</td>
<td>At least 7-10 days</td>
</tr>
</tbody>
</table>

*The frequency of dosing and duration of therapy can be adjusted, depending on the severity and duration of the patient’s bleeding episode.

**REFERENCES**