Case Report

Case of Severe Hemophilia

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ABSTRACT

Haemophilia is an X linked haemorrhagic disease due to mutation in the F8 or F9 gene. Males are generally affected. Haemophilia disease phenotype correlates with the residual activity of Factor VIII and can be classified as Mild (6 to 30%), Moderate (1 to 5 %) and Severe (<1%). In Moderate and severe forms, patients may have bleeding into Joints (Hemarthrosis), Soft Tissues, and Muscles after minor trauma or even spontaneously. Hematomas into muscle of distal parts of the limbs may lead to external compression of the arteries, veins or nerves that can evolve into compartment syndrome. These bleeding episodes are painful and may be life threatening in cases of oropharyngeal haemorrhage, retroperitoneal haemorrhage or bleed into the Central Nervous System.

Case :

A 38 years old male was admitted with complains of Pain in abdomen since 3 days, abdominal distension since 2 days, and constipation since 2 days. Patient was not able to walk and extend his right leg. Patient was a known case of Haemophilia and had history of repeated admissions. He had history of Subdural Haemorrhage in 2009. Patient was also a known case of Mental Retardation since birth. He was on Tab Olanzapine since 2012 due to psychiatric disorder.

Patient first admitted to a different hospital, and was referred for admission and further management to Government Medical College, Nagpur.

In the ER patient had severe pallor, was tachypnoeic, Pulse was 116/min regular, BP was 110/60 mmHg. Abdomen was distended with ecchymotic patch of size 5 x 5 x 3 cm over right lumbar region and right iliac fossa. Patient was drowsy, and not able to extend his right hip. Heart sounds were normal and Chest was clear.

Patient was immediately shifted to ICU and following investigations were done.

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Table 1 : **Laboratory Data**

Variable	Reference Range	Observed Value
Hemoglobin (g/dl)	11.0-15.0	3.7
TLC (per microliter)	4000-11000	19700
PLATELETS (per microliter)	1,50,000 - 4,50,000	1,53,000
HEMATOCRIT (%)	36-48	13.9
MCV (fl)	80.0-99.0	82.6
MCHC (g/dl)	32.0-36.0	26.6
PROTHROMBIN TIME (sec)	12.2 sec	13.4
International Normalised ratio	0.9-1.1	1.1
Activated partial Thromboplastin time (sec)	32.0 sec	>120.0 sec
Serum Urea (mg/dl)	15 45	67
Serum Creatinine (mg/dl)	0.5 - 1.5	0.8
Serum Sodium (mmol/l)	135-155	132
Serum Potassium (mmol/l)	3.5-5.5	3.7
Total Protein (g/dl)	5.5-7.5	5.5
Total Bilirubin (mg/dl)	0.2-1.2	1.7
Alkaline Phosphatase (IU/l)	36-200	150
Alanine Transaminase (U/l)	8-5	42

Aspartate Transaminase (U/l)	8-40	55
Serum Calcium (mg/dl)	8.7-10.4	7.0
Phosphate (mg/dl)	2.7-4.5	3.0
Uric Acid (mg/dl)	3.4-7.0	8.9
FACTOR VIII FUNCTIONAL ACTIVITY (%)	60.00-150.00	1.00

Patient's Factor VIII levels were reduced (in Severe haemophilia range). Also, he was severely anaemic and his aPTT was deranged.

Patient's CT Head (Plain) was done, which revealed-

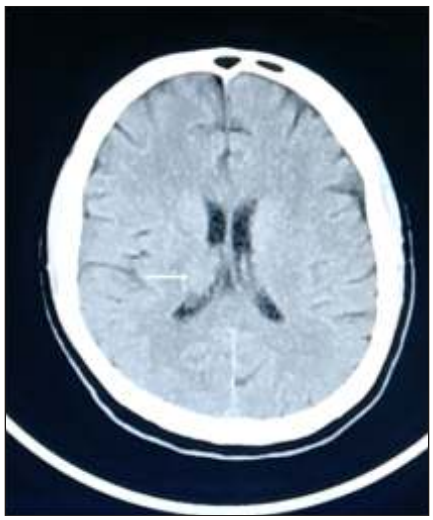

Fig. 1 : **CT Head Plain - Cyst-?, Hemorrhagic focus noted in 3rd Ventricle of size 6 x 5 mm (62 HU)**

Patient had a history of Head trauma (trivial) in 2012. The colloid cyst / ? Hemorrhagic focus in 3rd Ventricle might be attributed to the same.

Patient had no past records or CT Images of the episode, but relatives claim that he had to be hospitalised at that time and was administered Factor VIII concentrates. Patient's mental status became altered after the episode and he was subsequently started on anti- psychotics.

Patient also had CECT Abdomen + Pelvis done due to severe abdominal pain and discolouratrion around Right Iliac Fossa.

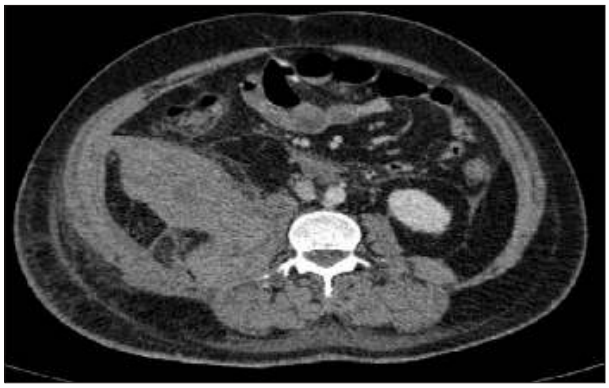

Fig. 2 : **CECT Abdomen + Pelvis- Hemorrhage / Hematoma noted anterior to and involving Right Ilio-psoas muscle extending to right antero-lateral abdominal muscle wall of approximate size 7.5 x 5.3 x 10 cm (190 cc).**

Patient was given Factor VIII concentrate and received a total dose 21000 units of Factor VIII over the next 2 weeks.

Patient's repeat Factor VIII levels were done, which showed Factor VIII levels to be 52%. aPTT levels were normalised.

Patient was then started on Tab Tranexa 250 mg BD.

Over the course of admission, patient became clinically better with normal consciousness, no abdominal pain and was now able to walk with support.

Discussion on Management :

The first treatment for haemophilia consisted of direct blood transfusion in 1840. In the 1950s and much of the 1960s, bleeding episodes were treated with fresh frozen plasma. Modern treatment started in 1965 with identification of the cryoprecipitate fraction of fresh frozen plasma by Judith Pool. Subsequently, technologies to separate factor VIII or IX from large pools of donor plasma resulted in freeze-dried, lyophilised factor VIII or IX concentrates, which improved patients' quality of life considerably.

Bleeding events are treated by replacement of the deficient coagulation factor to achieve adequate activity for haemostasis in all severity categories of haemophilia A. Treatment can be given as intravenous injection or continuous infusion.

Dosing strategies vary widely between providers and between countries and can depend on access to resources. Treatment should begin as early as possible because symptoms often precede objective evidence of bleeding. Drugs that hamper platelet function, such as Aspirin or Aspirin containing drugs, should be avoided. Factor VIII and Factor IX are dosed in Units. One unit is defined as amount of Factor VIII (100 ng/ml) in 1 ml of normal plasma. One unit of Factor VIII per kg of body weight increases the plasma Factor VIII level by 2%. The Dose required can be calculated using simple formula -

Factor VIII dose = (Target FVIII levels - Baseline FVIII levels) x Body Weight in kg x 0.5 unit/kg

Thus, 3500 units of Factor VIII will raise the circulating level to 100%. The FVIII half life of 8-12 hours requires injections twice a day to maintain therapeutic levels. Mild bleeds or superficial hematomas require initial therapy with Factor VIII levels of 30-50%. Large Hematomas or bleeds into deep muscles, require Factor VIII levels of 50% or even higher if the clinical symptoms do not improve, and factor replacement may be required for a period of one week or longer. The control of serious bleeds including those affecting oropharyngeal spaces, CNS, and the retroperitoneum require sustained protein levels of 50-100% for 7-10 days. Other option is to give Factor VIII by a continuous infusion of approximately 4 units/kg/hr. This method offers advantage of consistent levels, less frequent monitoring and decreased factor utilization. These infusions should not have an attached filter and the factor product should only be mixed with normal saline.

DDAVP is a synthetic vasopressin analog that causes transient rise in FVIII and von Willebrand (vWF), but not FIX, through a mechanism involving release from endothelial cells. Patients with moderate or mild Hemophilia should be tested to determine if they respond to DDAVP before a therapeutic application. DDAVP at doses 0.3 mcg/kg body weight, over a 20 min period, raises FVIII levels by 2-3 fold over baseline. DDAVP does not improve FVIII level in severe Hemophilia A patients because there are no stores to release. Repeated dosing results in tachyphylaxis and >3 consecutive doses become ineffective. If further therapy is indicated, FVIII replacement is required to achieve hemostasis. A complication of haemophilia treatment is formation of alloantibodies to Factor VIII or Factor IX. These inhibitors appear early in life, at 2 years of age, and after 10 cumulative days of exposure. Patients with high inhibitor titers do not respond to Factor VIII. In these cases the control of bleeding episodes is by using concentrates enriched for Prothrombin, FVII, FIX, FX and recombinant activated factor VII (FVIIa). For eradication of these inhibitory antibodies, the most effective strategy is immune tolerance induction based on daily infusion of missing protein until the inhibitor disappears. This may be required for a period of > 1 year.

New therapeutic options include Emicizumab. This is recombinant monoclonal antibody that binds to Factors IXa and X simultaneously, bringing the two molecules together and essentially substituting the scaffold role of FVIIIa as a cofactor for Factor IXa in activating Factor X.

Many new therapeutic options are in various phases of development for management of bleeding episodes and for prophylaxis of bleeding in haemophiliacs. Support by an experienced multidisciplinary team is indispensable to achieve optimum treatment as well as to promote compliance to various prophylactic regimens.

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