Abstract:
Fibrinogen deficiency is a very rare inherited bleeding disorder. There are three kinds of fibrinogen deficiency: afibrinogenemia, hypofibrinogenemia, and dysfibrinogenemia. Afibrinogenemia is a rare bleeding disorder with an estimated prevalence of 1:1,000,000. It is an autosomal recessive disease resulting from mutations in any of the 3 genes that encode the 3 polypeptide chains of fibrinogen and are located on the long arm of chromosome 4. Spontaneous bleeding, bleeding after minor trauma and excessive bleeding during interventional procedures are the principal manifestations. Replacement therapy is the mainstay of treatment of bleeding episodes in these patients and plasma-derived fibrinogen concentrate is the agent of choice. Cryoprecipitate and fresh frozen plasma are alternative treatments that should be used only when fibrinogen concentrate is not available.

Keyword:
Afibrinogenemia, bleeding disorder, Cryoprecipitate

Case history:
One year old male child, third born of third degree consanguineous parentage presented with swelling around the left eye following a trivial fall. The swelling progressively increased in size over six days. There was no swelling elsewhere; there were no obvious signs of infection or bone injury. The child had an uneventful antenatal and natal history. The postnatal history was significant for prolonged bleeding from the umbilical stump requiring transfusion but with no further evaluation. He also had another episode of spontaneous gum bleed at 8 months of age. The family history was negative for any similar illness. The child was developmentally normal. The child had not been immunised. On examination, the child’s sensorium was normal, he was not pale or icteric, had periorbital hematoma around the left eye. He had proptosis and difficulty opening the left eye. Initial investigations showed normal platelet count, normal bleeding time and a prolonged clotting time. His liver function tests were within normal limits. Samples were drawn for PT, aPTT. In view of prolonged clotting time child was started on FFP transfusion 10ml per kg per day. USG left orbit showed thick echogenic fluid and CT orbit was suggested which in turn showed erosion of floor of orbit with orbital widening- possibility of extra conal soft tissue mass? Rhabdomyosarcoma. As there was no evidence of optic nerve compression and decrease in the hematoma with FFP transfusions, radiologist and medical oncologist suggested follow up CT after 2 weeks. PT, aPTT results were found to be abnormal. Based on the course of the child’s illness, common pathway clotting factors deficiency (factor X, V, II, I, XIII) was suspected and a quantitative analysis was done which showed low levels of factor I (14 mg % of fibrinogen against a normal range of 200-400 mg%). Thus we arrived at a diagnosis of congenital afibrinogenemia. The child had no new bleeds and the existing bleed resolved with FFP transfusion. He was discharged and under follow up for periodic plasma transfusion.

Discussion
Afibrinogenemia (fibrinogen <20 mg/dL) is a rare bleeding disorder with an estimated prevalence of 1:1,000,000. It is an autosomal recessive disease. Afibrinogenemia results from mutations in any of the 3 genes located on chromosome 4q that encode the 3 polypeptide chains of fibrinogen. These mutations affect the synthesis, assembly, intracellular processing, stability or secretion of fibrinogen. Fibrinogen plays an important role in clot formation through its conversion to fibrin by the action of thrombin. It is also important in primary haemostasis since it contributes to platelet aggregation by binding to glycoprotein Ib/IIa on the activated platelet surface. The commonest manifestations of afibrinogenemia are umbilical stump bleeding which can be life threatening and bleeding from mucosal surfaces, particularly menorrhagia, epistaxis and bleeding in the oral cavity. Musculoskeletal bleeding including hemarthroses is observed in around half of the patients. Bleeding from the gastrointestinal and urinary tract is less frequent whereas intracranial bleeding is rare. Hemoperitoneum and haemorrhagic corpus luteum following the rupture of a follicle during ovulation are other rare manifestations. The bleeding tendency is highly variable in afibrinogenemia (ranging between very few up to several episodes/year) even among patients with the same mutation. The presence of modifier genes yet unidentified has
been implicated as an explanation for this variability. Besides spontaneous bleeding, bleeding after minor trauma and excessive bleeding during interventional procedures are other principal manifestations of afibrinogenemia. Replacement therapy is the mainstay of treatment of bleeding episodes in patients with afibrinogenemia and includes plasma-derived fibrinogen concentrate, cryoprecipitate and fresh frozen plasma (FFP). The only readily available sources of fibrinogen are fresh frozen plasma and cryoprecipitate. Though Fibrinogen concentrate is the replacement therapy of choice in patients with afibrinogenemia Cryoprecipitate is currently the most practical source for replacement and contains approximately 200 mg of fibrinogen per bag of cryoprecipitate. Haemorrhagic symptoms are usually controlled by initially achieving plasma levels of 80 to 100 mg/dL and maintaining this level above 50 to 60 mg/dL until the bleeding subsides. Since the half-life of fibrinogen is approximately 4 days, alternate day administration should be sufficient in the absence of consumption.

PROGNOSIS:
Symptoms in patients with afibrinogenemia are not as severe as those seen in the classic haemophilic disorders. Intracranial bleeding is rare although recurrent episodes are rarely reported.

CONCLUSION:
Fibrinogen deficiency states (afibrinogenemia and hypofibrinogenemia) and hereditary functional abnormalities of fibrinogen (dysfibrinogenemias) are infrequently encountered but should be considered when a prolonged PT, aPTT is found in a patient with a bleeding history who is otherwise essentially healthy.

BIBLIOGRAPHY: