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CASE REPORT

Congenital Hypofibrinogenemia Detected during Preoperative Workup for Major Cardiac Surgery

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ABSTRACT

Afibrinogenemia or hypofibrinogenemia is a quantitative defect in fibrinogen. It is a rare disease with estimated frequency of 1 in 1,000,000 population. Routine preoperative screening tests of coagulation disorders are insufficient to detect subtle disorders of fibrinogen. Herein, we report a child who was supposed to undergo open cardiac surgery for a large atrial septal defect. Preoperative coagulation screening tests revealed minimal prolongation of prothrombin time which made us do further work-up. Finally, she was diagnosed with hypofibrinogenemia who was suggested to be congenital.

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Introduction

Fibrinogen is a 340-kD glycoprotein synthesized in the liver which circulates in the plasma at a concentration of 2-4 g/L with a half-life of 4 days.[1-3] Fibrinogen is converted to fibrin, with formation of fibrin clot in the final step of coagulation cascade. Along with this function, other functions of fibrinogen include non-substrate thrombin binding, platelet aggregation, and initiation of fibrinolysis.[3, 4] Exposure of its thrombin-binding sites after fibrin clot formation promotes the antithrombotic properties of fibrinogen.[3] Therefore, fibrinogen disorders may present with either a bleeding or a thrombotic event.[5] Afibrinogenemia and hypofibrinogenemia are quantitative defects in fibrinogen. Dysfibrinogenemia refers to functional abnormalities (qualitative) of fibrinogen at normal concentrations.[1, 3] Afibrinogenemia is usually diagnosed in the newborns when they present with umbilical cord bleeding.[3, 4] Individuals with hypofibrinogenemia are frequently asymptomatic, but may be first diagnosed at the time of trauma or a surgical procedure.[3, 4] We report a child who was supposed to undergo open cardiac surgery for a large atrial septal defect (ASD). Preoperative minimal prolongation of prothrombin time (PT) made us search for detecting a coagulation disorder. Laboratory tests indicated low fibrinogen levels suggestive of congenital

Table 1: Laboratory Investigations of the patient

Test Name	Result	Reference Range
Haemoglobin	13.4 gm/dl	13-15 gm/dl
White blood cells	4600 /mm3	400-1100 cells/mm3
Platelet count	215000 /mm3	150000-400000/mm3
PT(Prothrombin Time)	16.0 sec	12-14 sec
PT Control	12.0 sec	
APTT Clot based	36.0 sec	26-36 sec
APTT control	30.0 sec	
Clauss fibrinogen assay	92.0 mg/dL	180-400 mg/dL
Fibrinogen Antigen	70.0 mg/dL	150-400 mg/dL
Thrombin Time	41.0 sec	17-21 sec
Factor VIII Assay (Clot based)	183.0 %	70-150 %
VWF Antigen	104.93 %	60-150 %
VWF:Ristocetin cofactor	75.92 %	50-200 %
Platelet Aggregation Study (Light transmission aggregometry) (LTA)		
ADP	76.4 %	50-100 %
Arachidonic Acid	80.4 %	50-100 %
Collagen	79%	50-100 %
Ristocetin	75.4 %	50-100 %
Factor 9 assay (clot based)	155	70-150
Factor 13 assay (chromogenic)	139	70-150

hypofibrinogenemia.

Case Report

A child with a large ASD with left to right shunt was referred for surgical repair through open heart surgery. The only abnormal preoperative laboratory test was a prolonged PT. Further work-up was performed for the patient. Since PT and thrombin time (TT) were also found to be prolonged, the possibility of low fibrinogen level was considered. Absolute fibrinogen level was checked which was very low and diagnosis of congenital hypofibrinogenemia was confirmed (Table 1). Her fibrinogen level was low suggestive of congenital hypofibrinogenemia. The child underwent cardiopulmonary bypass and ASD was closed with autologous pericardial patch. Intraoperative and post-operative period was uneventful. There were no bleeding events during the surgery. Consents for reporting was obtained.

Discussion

Afibrinogenemia occurs in homozygotes whereas hypofibrinogenemia usually is a finding of heterozygotes.[1] Quantitative disorders of fibrinogen are generally inherited as autosomal recessive, whereas qualitative dysfibrinogenemias are inherited as autosomal dominant disorders in most cases.[4] The frequency of afibrinogenemia is estimated to be 1-2 cases per million population with a high rate of consanguinity. [3, 5] Afibrinogenemia is usually diagnosed in the newborns when they present with umbilical cord bleeding.[3, 4] Individuals with hypofibrinogenemia are generally asymptomatic, but may be first diagnosed at the time of the trauma or surgical procedures that result in mild to moderate bleeding depending on their plasma fibrinogen levels.[3, 4] Patients with hypofibrinogenemia remain asymptomatic until fibrinogen levels decrease to 60 mg/dL.[1] The absence of bleeding in these patients can be attributed to the presence of von Willebrand factor, which binds to the glycoprotein complex on platelets and provides a backup mechanism for platelet aggregation, serving to replace fibrinogen. In addition, a small quantity of platelet fibrinogen may also be a facilitator leading to the absence of bleeding symptoms.[6] In a study of 102 patients with congenital dysfibrinogenemia, Zhou et al. found bleeding symptoms in 27.5% of them and thrombosis in 3.9%, while 68.6% of patients were asymptomatic.[7] In a Medline research including 62 publications, seven of 226 babies with congenital coagulation defects were found to have fibrinogen deficiency. Five of them had umbilical cord bleeding, one had hematoma and two developed bleeding following circumcision.[8] Hypofibrinogenemia can be confused with mild haemophilia, since hemarthrosis may develop in 20% of these patients.[6] Central nervous system bleeding is rare in congenital hypofibrinogenemia and out of 100 bleeding patients due to head injury, only seven (7%) patients had hypofibrinogenemia.[9] Minnis and Griffin reported a case of congenital hypofibrinogenernia associated with congenital heart disease (pulmonic stenosis and partial anomalous pulmonary venous drainage).[10] Our child had ASD associated with hypofibrinogenemia. Diagnosis of fibrinogen disorders is made by clinical history, physical examination and laboratory investigations. Since fibrinogen is a common pathway plasma protein, both prothrombin time (PT) and activated partial thromboplastin time (aPTT) are expected to be prolonged. In addition, TT would be prolonged when low levels of fibrinogen are detected. An assay of functional/antigenic fibrinogen ratio will help distinguish qualitative defects from quantitative deficiencies. When the functional activity level is low, dysfibrinogenemia or hypodysfibrinogenemia should be considered. If both the activity and antigen levels are proportionally low, a quantitative deficiency is more suggested. Rani

and Gopinath reported a case of prolonged Activated Coagulation Time (ACT) during cardiac surgery caused by preoperatively undiagnosed hypofibrinogenemia. ACT has become the standard for monitoring heparin anticoagulation during cardiac surgery.[1] It is not capable of differentiating between the absence of coagulation factors and the presence of heparin.[1] The present case report emphasizes that minor coagulation defects may not be detected by routine coagulation tests recommended for patients undergoing cardiac surgery. Cardiopulmonary bypass produces significant changes in the coagulation factors that exaggerate any preoperative deficiencient state. So, it can be assumed that routine preoperative screening tests of coagulation are insufficient to detect subtle disorders of fibrinogen.[1] Fibrinogen deficiencies are not detected by PT and APTT which are often normal provided some fibrinogen is available for clot formation,[2] but TT and reptilase time are more sensitive to abnormalities of fibrinogen than the PT and APTT.[2] In general, screening for a mild fibrinogen deficiency or dysfibrinogenemia often requires a Clauss fibrinogen assay and a thrombin time, with or without a reptilase time, to determine if there is a potential discrepancy between the amount of fibrinogen and its function.[2] In afibrinogenemia or hypofibrinogenemia, moderate to severe bleeding is treated with a fibrinogen-rich factor concentrate, fresh frozen plasma or cryoprecipitate.[8] The homeostatic level of fibrinogen is above 60 mg/dL. In severe life threatening haemorrhage, fibrinogen should be replaced to reach to a level of at least 100 mg/dL.

Conclusion

A thorough coagulation work up should be performed for a child who is subjected to open cardiac surgery to prevent unnecessary bleeding due to clotting factor deficiencies.

Conflict of Interest: None declared.

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