Case Report

Purplish Skin Lesions and Intracranial Bleeding with Prolonged Coagulation Assays: Bleeding or Thrombosis?

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Keywords

Purpura fulminans, intracranial bleed, Protein C deficiency, Purplish skin lesions

Background

Coagulation profile [Prothrombin Time (PT) and activated Partial Thromboplastin Time (aPTT)] help in characterisation of defects in intrinsic, extrinsic and common pathways of coagulation. We present a case wherein an error in interpretation of coagulogram led to withholding of primary therapeutic modality.

Case Report

A 15 months old boy was admitted with the history of palpable purplish lesions over the abdominal wall (Figure 1) and legs. Family history was non-contributory.

He was born by normal vaginal delivery to a primigravida mother and had no birth asphyxia. On day 2 of life, he had similar purplish lesions in gluteal regions and bilateral calves and multiple episodes of right focal seizures. Investigations were suggestive of anemia (Hb - 8 gm/dL), thrombocytopenia (Platelet count - 40,000/mm^3) and elevated PT (50 seconds). aPTT was not available. Computerized Tomography (CT) done on day 3 of life was suggestive of intracerebellar bleed extending into vermis and all the ventricles with acute subarachnoid haemorrhage and obstructive hydrocephalus (images not available). The baby was given Vitamin K and Fresh Frozen Plasma (FFP) transfusions with a suspicion of hemorrhagic disease of newborn. Skin lesions improved over next few days. Platelet counts and PT normalised. MRI done at 3 months of age showed medullary venous congestion and periven-tricular leukomalacia due to presumable thrombotic angiopathy of deep venous system (Figure 2A-E).

Over the next few months, the baby was noticed to have global developmental delay with myoclonic spasms. A repeat MRI showed further dilatation of lateral ventricles due to destruction of ischemic white matter (Figure 2F).

Investigations done at the age of 15 months revealed both PT and aPTT to be more than 2 minutes with a platelet count of 44,000/µL. Fibrinogen levels were extremely low. Past history of intracranial bleed with prolonged PT and aPTT had led the treating team to think of a “bleeding disorder”. Genetic test was requested for, with a clinical possibility of “afibrinogenemia” and the baby was started on FFP

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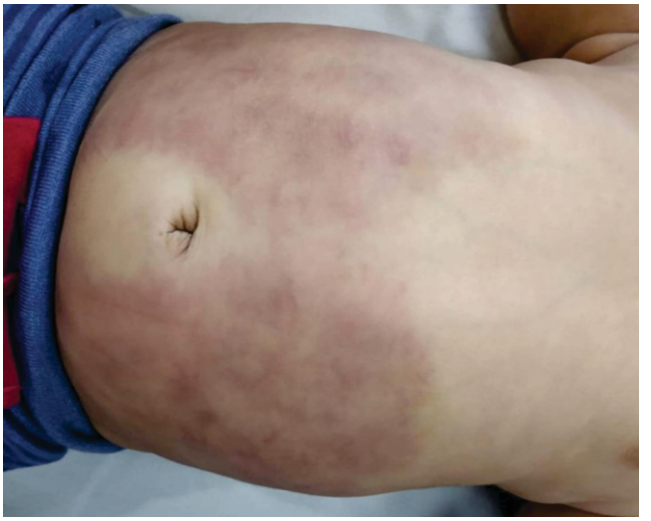

Figure 1: Purplish skin lesions over abdominal wall

infusions. The FFP transfusions led to normalization of PT, aPTT and platelet count, however the d-Dimer levels continued to be high at 30,926 ng/ml and skin lesions did not show any improvement. A shift to cryoprecipitate transfusions resulted in prolongation of both PT and aPTT to more than 2 minutes.

Reanalysis of clinical and laboratory picture suggested a possibility of Disseminated Intravascular Coagulation (DIC). Chronic history and absence of any features of sepsis led to a possibility of congenital prothrombotic disorder. Low Molecular Weight Heparin (LMWH) and FFP transfusions were initiated. Skin lesions and coagulogram abnormalities showed complete improvement within 1 week. Genetic analysis revealed homozygous c.169C>T(p.Arg57Trp) mutation in exon 3 of PROC gene suggesting "severe Protein C deficiency". Because of nonavailability of protein C concentrate, he continues to be on LMWH with normal PT, aPTT and d-

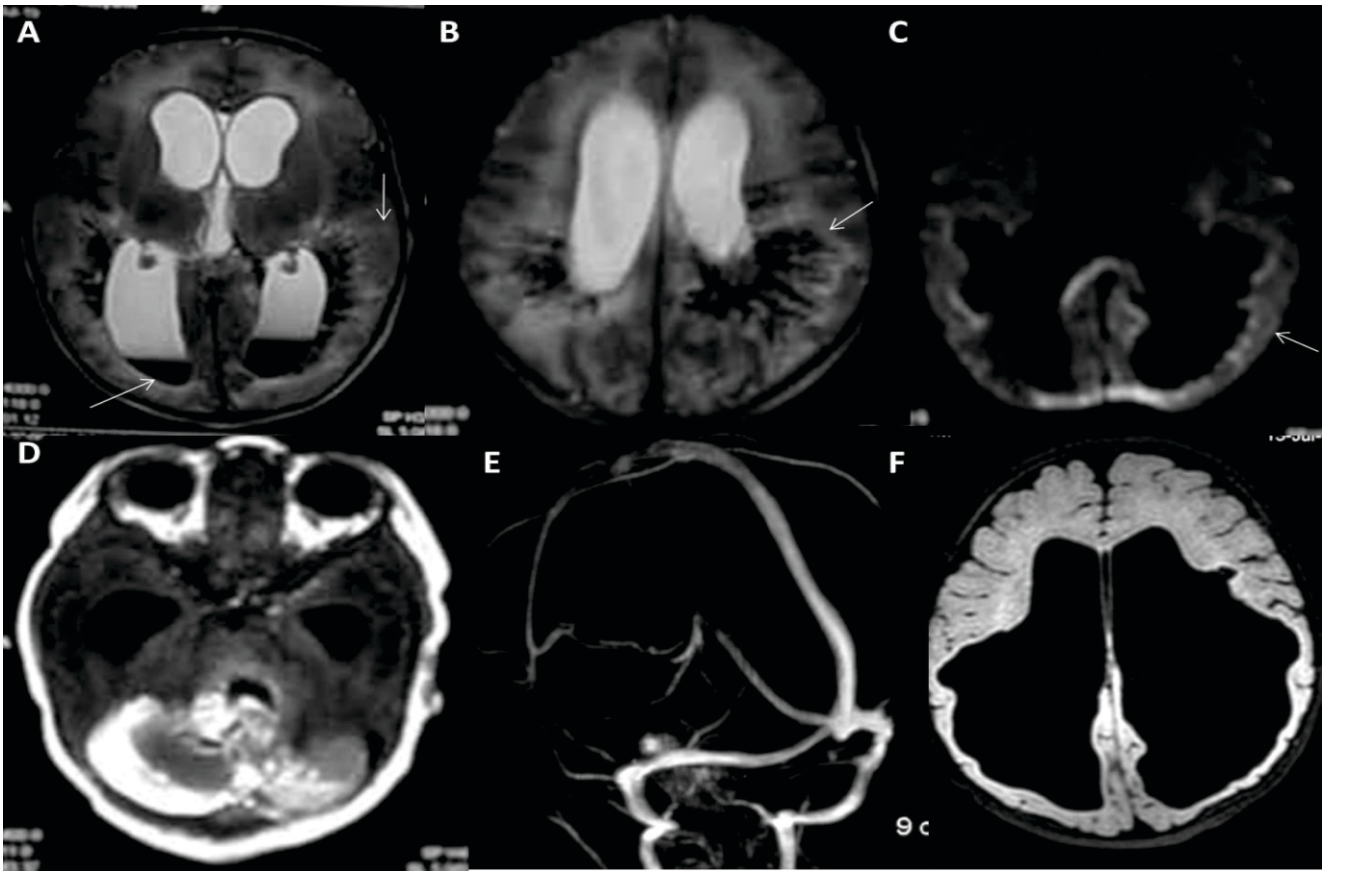

Figure 2: Medullary venous congestion and periventricular leukomalacia due to presumable thrombotic angiopathy of deep venous system. Multifocal lesions suspected in view of cerebellar bleeds. A &B: T2 weighted images showing hydrocephalus with intra-ventricular bleed with layering in lateral ventricles (arrow A). Radiating periventricular linear signal presumably due to congested medullary veins (arrows B and C). C: Diffusion weighted image showing periependymal diffusion restriction indicating deep white matter ischemic damage (arrow). D: T1 weighted images showing haemorrhages in posterior fossa possibly secondary to deep venous thrombosis or multifocal thrombotic lesions. E: MR venography showing patent major venous sinuses . F: FLAIR (Follow up) image showing further dilatation of lateral ventricles due to destruction of ischemic white matter

Dimer levels.

Discussion

Prolongation of both PT and aPTT is seen in common pathway defects (Table 1) (afibrinogenemia, severe deficiencies of factor II, V, X) or in the combined deficiency of Vitamin K dependent factors (liver disease and haemorrhagic disease of the newborn)[1]. An erroneous diagnosis of afibrinogenemia was thought of due to history of intracranial bleed in newborn period and prolonged PT and aPTT with low fibrinogen levels.

Thrombocytopenia along with prolonged PT and aPTT and very high d-Dimer levels are suggestive of DIC[1]. Low fibrinogen is a secondary phenomenon due to excessive consumption. Detection of excessive thrombosis warrants evaluation for prothrombotic conditions, which may be both genetic and acquired[2]. Very young age at onset makes genetic conditions more likely, though acquired causes like antiphospholipid antibody syndrome have also been described[3]. Deficiency of natural anticoagulants such as protein C, protein S and antithrombin III results in excessive thrombosis. Maximum risk of thrombosis in neonatal age is seen with protein C deficiency[4].

Protein C is a vitamin K dependent serine protease synthesized by liver[5]. Binding of thrombin to thrombodulin at the time of thrombosis causes activation of protein C in the presence of protein S. Activated protein C inhibits factor Va and VIIIa causing inhibition of Factor X and Factor IX activation, respectively and hence acts as a natural anticoagulant.

Inheritance is autosomal dominant and individuals with one altered copy of PROC gene have mild deficiency of protein C. Autosomal recessive inheritance is seen in individuals with severe deficiency with a prevalence of 1 in 5,00,000 individuals[5].

Clinical manifestations vary with severity of deficiency. Mild deficiency may be asymptomatic. Adults with moderate deficiency may develop deep vein thrombosis or pulmonary embolism[5]. Patients with severe deficiency can present with purpura fulminans and DIC like picture in early childhood[6].

Intracranial bleeding can occur due to venous-sinus

Table 1. Interpretation of common abnormalities in coagulogram

Finding	Interpretation	Cause
Prolonged PT and normal aPTT	• Extrinsic pathway defects	• Factor VII
Prolonged aPTT and normal PT	• Intrinsic pathway defects	• Factor VIII • Factor IX • Factor XI No hemostatic problems • Factor XII • High-molecular-weight kininogen • Prekallikrein
	• Inhibitors	• Antiphospholipid syndrome • Heparin
Prolonged PT and aPTT with normal platelet count	• Deficiency of factors in Extrinsic + Intrinsic pathway, Common pathway, or all three pathways	• Liver disease (Fibrinogen and factors II, V, VII, IX, X, XI and XII) • Vitamin K deficiency or antagonists (Factors II, VII, IX and X) • Factor V • Factor X • Factor II • Fibrinogen
	• Inhibitors to factors in Extrinsic + Intrinsic pathway, Common pathway, or all three pathways	• Direct thrombin inhibitors • Excess heparin in the sample • Lupus anticoagulant • Nonspecific inhibitors as in lymphoproliferative disorders and monoclonal gammopathy
Prolonged PT and aPTT with reduced platelet count	• DIC like picture	• Sepsis/trauma/malignancy • Prothrombotic conditions

distension and congestion secondary to thrombosis within the venous system of central nervous system or secondarily due to consumptive coagulopathy[7]. Presence of bleeding in such a setting should not lead to an erroneous diagnosis of "primary bleeding disorder", as such patients may benefit from anticoagulation.

Diagnosis is established by estimating protein C levels and activity in serum. This method can be particularly challenging in newborns and young children because of physiologically low levels in infancy, further reduction in levels during acute episodes of thrombosis, and non-availability of nomograms for young children[5]. Acquired protein C deficiency can occur due to reduced synthesis (vitamin K deficiency, liver disease), excessive consumption (DIC due to other causes) and excessive loss (nephrotic syndrome). In such settings, genetic analysis can be very useful in making a diagnosis.

Treatment depends on severity of deficiency. Severe deficiency of protein C warrants lifelong treatment. Replacement of deficient protein C can theoretically prevent thrombosis. Protein C concentrate is available in some countries. In countries where protein C concentrate is not available, FFP can be used[8]. A very short half life (8 hours) necessitates transfusions every 8-12 hours. Administration of FFP transfusions in the index child produced a partial response by normalizing PT and aPTT. Cryoprecipitate, being poor in protein C, should not be used for replacement[9].

Prevention of further thrombosis can be achieved by anticoagulation with LMWH or oral anti-coagulants like warfarin. Warfarin should be used with caution as it can induce skin necrosis by further reducing levels of vitamin K dependent factors including protein C and causing thrombosis[7,10].

Lessons Learnt

Prolonged PT and aPTT with thrombocytopenia suggest a DIC like picture. Raised d-Dimer levels further support the possibility of extensive thrombosis instead of primary bleeding. All children with DIC like picture on coagulogram need to be investigated for congenital and acquired causes of thrombosis. Congenital prothrombotic disorders can present with "DIC like picture" in infants and young children.

Intracranial bleed can be a rare presentation of venous sinus thrombosis and may warrant anticoagulation. Replacement of deficient protein C and/or prevention of ongoing thrombosis by giving anticoagulation are the cornerstone of treatment in patients with protein C deficiency despite "prolonged PT and aPTT and low fibrinogen", which is a secondary effect of extensive thrombosis.

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