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Unusual Cause of Recurrent Intra Cranial Bleeding in An Infant

KEYWORDS: Vitamin K, PT, aPTT, intra cranial hemorrhage, coagulation factors

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ABSTRACT *Vitamin K dependent coagulation factor deficiency is a rare autosomal ressessive disorder presenting as bleeding manifestations including intracranial hemorrhage with prolonged prothrombin time and activated partial thromboplastin time. Initially the diagnosis may be confused with hemorrhagic disease of newborn. We describe a patient with Vitamin K dependent Coagulation factor II, VII, IX and X deficiency with recurrent intra cranial hemorrhage.*

Introduction:
Combined deficiency of Vitamin K dependent Coagulation factors (VKCFD) is a rare bleeding disorder. The first case of VKCFD was described in 1966 in an infant girl with multiple bruises and hemorrhages. She had prolonged PT and aPTT, which corrected on mixing 1:1 with normal plasma, indicating factor deficiency. She was found to have low or undetectable levels of Vitamin K dependent Coagulation factors II, VII, IX and X without any evidence of hepatic disease or malabsorption (1). This disorder is caused by mutations in the genes of either gamma-glutamyl carboxylase or vitamin K2,3-epoxide reductase complex. Additional VKCFD cases and pedigrees have been reported over the years (2-5). We report an infant with recurrent intracranial bleeding secondary to Vitamin K dependent Coagulation factor deficiency.

Case report
A two and half month old boy was brought with history of fever and cold with excessive cry for 2 days, associated with multiple episodes of convulsions of 1 day duration. He was apparently well before onset of these symptoms. He was a 3rd child of a second degree consanguineous parentage. First child was 6 yrs old healthy girl, second was a male child, who had similar history and died at the age of 2 months.

He was born in a hospital by normal vaginal delivery with a weight of 2900 gms. There was no history of cephalhematoma, prolonged bleeding from cord or hyperbilirubenemia in postnatal period. Vitamin K was not given at birth. He was on exclusive breast feeding till the illness. On examination he was lethargic, had bulging anterior fontanellae, severe pallor and echymotic patches over both the ankles. A provisional diagnosis of Late Hemorrhagic disease with intracranial bleeding was considered and investigated.

His investigations had revealed hemoglobin of 4.4 gms\dl with a total count of 15,200 and differential count of N-55%, L-36%, E-1%, M-8%, Platelet count of 8.04 lakhs. Prothrombin time was 108 seconds with a control of 13 seconds, aPTT of 180 seconds and control of 30 seconds and INR of 10. Liver function tests showed serum total bilirubin of 3.05 mg, directly reacting bilirubin of 1.78 mg, ALT-56.5 IU\L, AST-46.7 IU\L, Total serum proteins of 6.36 gms, Albumin of 2.94gm, Globulin of 3 gm, Alkaline Phosphatase - 944.3 IU. In view of bulging anterior fontanellae and severe pallor a CT brain was done which showed Left fronto temporal subdural hemorrhage with left anterior cerebral artery and middle cerebral artery infarct and a midline shift of 1.3 cms to left with mass effect (Fig1). He was managed with measures including packed cell transfusion, Vitamin K injections, FFP transfusion and anticonvulsants. He required mechanical ventilation for poor general condition and poor respiratory efforts. His condition improved with conservative management, PT and aPTT normalized after Inj Vitamin K and FFP transfusions, and he was weaned of ventilator and discharged from hospital with anticonvulsants and an advice for follow up.

Six weeks later patient came back with history of decreased activities and two episodes of generalized tonic clonic seizures. His hydration status was normal, anterior fontanellae was at level and pulsatile, with severe pallor and lethargy. There were no focal deficits but had generalized hypotonia with brisk deep tendon reflexes. He had Hemoglobin of 5.6 gms\dl, TC of 11,450 and differential count of N-57%, L-34%, E-3%, M-6%, Platelet count of 5.1 lakhs. Liver function studies were normal with Serum total bilirubin of 0.9 mg, directly reacting bilirubin of 0.3 mg, ALT-18 IU\L, AST-24 IU\L, Total serum proteins of 6.36 gms, Albumin of 3.64gm. His coagulation studies showed PT of 119 seconds (control-12 seconds) and aPTT of 168 seconds (control-30 seconds). A repeat CT scan brain revealed left fronto-temporo-parietal chronic subdural hematoma. In view of prolonged PT and aPTT, a mixing study was done which corrected with 1:1 plasma, indicating a factor deficiency. A detailed coagulation factor assay was carried out (Table 1), which showed decreased levels of Vitamin K dependent coagulation factors to variable degree. An ultrasound abdomen done was showing left sided ectopic kidney, the importance of which was uncertain. The child's condition stabilized, including PT and aPTT after Vitamin K and FFP transfusions. He was discharged and regularly followed up. Presently the child is 8 months old and has global developmental delay.

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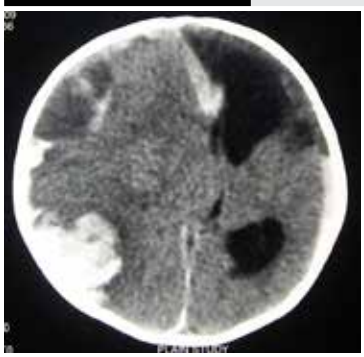

Fig1. CT brain showing left fronto-temporo-parietal subdural hemorrhage with left ACA and MCA infarct, and a midline shift of 1.3 cms to left with mass effect.

Table 1. Investigations showing Anemia, prolonged PT, aPTT and varying degrees of low levels of Vitamin K dependent clotting factors.

Tests	Result value	Normal
Hemoglobin	5.6 gm/dl	(12-16gm/dl)
Platelet count	6.8 lakh/mm2	(1.5-4 lakh/mm2)
Prothrombin time Test	-108 sec	(12-14 sec)
	Control -13 sec	
Partial Prothrombin time Test	-180 sec	(26-36 sec)
	Control -30 sec	(26 sec)
Mixing study: Patient+Control	Corrected 33 sec	
Thrombin time	10 sec	(10-12sec)
Fibrinogen	491 mg %	(200-400)
F II activity	57%	(70-120)
F V activity	120%	(70-120)
F VII activity	30%	(70-120)
F VIII activity	200%	(60-150)
F IX c activity	1.6%	(30-113)
F X activity	40%	(70-120)
F XI c activity	88%	(70-120)

Discussion

Vitamin K is a cofactor for hepatic carboxylation of glutamic acid residues in a number of proteins, resulting in its conversion to gamma-carboxyglutamic acid (Gla). This is critical for the activation of vitamin K-dependent clotting factors II, VII, IX and X in the coagulation cascade. VKCFD is caused by mutations in the genes of either gamma-glutamyl carboxylase or vitamin K2,3-epoxide reductase complex. These two proteins are necessary for gamma-carboxylation, a post-synthetic modification that allows coagulation proteins to display their proper function. The gamma carboxylation is catalyzed by hepatic gamma-glutamyl carboxylase, which requires reduced vitamin K (KH2) as a cofactor. During the gamma-carboxylation reaction, KH2 is converted to vitamin K epoxide (KO), which is recycled to KH2 by the vitamin K epoxide reductase enzyme complex (VKORC1). Two subtypes depending on mutations of two enzymes of the vitamin K cycle have been identified: VKCFD type1 is defined by defective GGCX activity (located on chromosome 2p12), first reported in Devon Rex cats (7), while VKCFD type 2 derives from functional deficiency of VKORC1 (located on chromosome 16p11.2) (6,7, 11).

VKCFD patients have markedly prolonged PT, and partial thromboplastin time that correct with plasma mixing. Factor II, VII, IX and X activity levels variably reduced, usually very low in severe cases and partially improve with Vitamin K treatment of these patients. Proteins induced in Vitamin K absence (PIVKA-II, under-carboxylated prothrombin) are increased. Protein C, S and Z activities are also reduced; however, thrombotic events seem to be much less common (10, 11).

The severity of hemorrhagic manifestations varies from mild bleeding to fatal intra cranial bleeding. Severe bleeding is usually associated with very low factor levels. The clinical presentation may be more severe in patients if there is concomitant acquired Vitamin K deficiency and a milder clinical presentation in patients treated with therapeutic doses of Vitamin K. The routine administration of Vitamin K to new born babies may delay the diagnosis of VKCFD. Skeletal defects have also been reported in some patients, likely due to defective gamma carboxylation of certain non-haemostatic bone matrix proteins or from Vitamin K interactions with other target genes in osteoblasts (8, 9).

Diagnosis:

Diagnosis of VKCFD depends on the persistence of bleeding manifestations and reduced levels of Vitamin K dependent coagulation factors and anticoagulation factors. Warfarin ingestion, malabsorption and liver diseases must be ruled out. Genotyping for VKORC1 (5kb) and GGCX (13kb) is possible in selected research laboratories. Serum Vitamin K and Vitamin K epoxide levels also can be measured in research laboratories. Vitamin K epoxide is normally undetectable in serum but is elevated in VKCFD2 following Vitamin K supplementations (10).

Management:

Management includes large doses of oral Vitamin K, which may partially correct the low factor levels in severely affected patients to about 15-20%. These partially corrected factor activities resemble milder cases of VKCFD (5, 7). Large doses of parenteral Vitamin K do not always correct deficient factor activities, and there is clear evidence that molecules are not fully carboxylated by such treatment (2, 8). Fresh frozen plasma infusions for surgical procedures and overt hemorrhage are advised. VKCFD patients often require multiple doses of Fresh frozen plasma. In addition, prothrombin complex concentrates and combination therapy with recombinant activated FVII and vitamin K supplementation may constitute alternative treatment options.

Prognosis:

Prognosis of VKCFD can be guarded if it manifests in the early infancy, especially with intra cranial bleeding, which can result in permanent neurological damage and developmental disability (5, 6, and 11). Mild to moderate cases may have favorable outcome over period of time. Regular Vitamin K dosing may maintain hemostasis. Early intervention with appropriate treatment and prevention modalities would probably improve the prognosis. As noted previously, factor levels partially improve with vitamin K therapy, and regular vitamin K dosing may maintain hemostasis to a variable extent.

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