Letter to the Editor

Coagulation status in a-βetalipoproteinemia

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A-betalipoproteinemia is a rare disorder of lipoprotein metabolism, characterized by abnormal serum lipoprotein levels, absence of chylomicrons, reduced levels of lipid soluble vitamins, malabsorption and peripheral acanthocytes. Among the various clinical manifestations of this disorder, consequences related to malabsorption of lipid soluble vitamins and especially vitamin E, are the most clinically important. Vitamin K is a key factor, significantly involved in hemostatic mechanisms[1]. There are limited data concerning the levels of plasma Vitamin K-dependent proteins and anticoagulant proteins in patients with a-betalipoproteinemia.

We report here the results of the determination of both, plasma Vitamin K-dependent procoagulant and plasma Vitamin K-dependent anticoagulant proteins in a patient with a,betalipoproteinemia.

PATIENT - RESULTS

A previously described female patient with a-betalipoproteinemia[2] was tested for various plasma protein involved in blood coagulation and fibrinolysis. She was tested while she was receiving only Vitamin E parenterally in an effort to reduce the severity of neurological symptoms.

We determined all plasma proteins with functional assays on an automatic analyzer STA Combact, Diagnostica Stago. FV (Leiden) and FII (G20210A) mutations were also determined using standard polymerase chain reaction (PCR) assays.

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The results are shown in Table 1. In more detail, the levels of Vitamin K-dependent plasma proteins involved in blood coagulation were normal for factor IX, almost normal for factor II (69%. vs 70%) and low for factors VII and X (37% and 43% vs 70% respectively), compared to the lowest limit of our laboratory. Other plasma

Table 1. Plasma Vitamin K-dependent proteins levels involved in blood coagulation and Plasma Vitamin K-dependent anticoagulant proteins levels in a patient with a-betalipoproteinemia.

Factor	Result
Factor I (Fibrinogen)	373 mg/dl (200-400)
Factor II (Prothrombin) *(Vit K-dependent zymogen)*	69% (70-120)
Factor V	69% (70-120)
Factor VII *(Vitamin K-dependent zymogen)*	37% (70-120)
Factor VIII (Antihemophilic factor)	200% (60-150)
Factor IX *(Vitamin K-dependent zymogen)*	66% (60-150)
Factor X *(Vitamin K-dependent zymogen)*	43% (70-120)
Factor XI	77% (60-140)
Factor XII	64% (60-140)
Von Willebrand factor	141% (50-160)
Antithrombin III	118% (80-120)
Protein C	130% (70-130)
Protein S	59% (65-140)
Free protein S	56% (60-140)
Plasminogen	116% (80-120)
LP (Lupus anticoagulant)	3.3sec (0-8)
Prothrombin time	62% 16.5 sec, 12.2 Ref. T 12.2 sec
INR	1.45
APTT	29.8 sec (27.0-40.0)
APC resistance	158 sec (110-300)

(Numbers in parentheses are normal values)

proteins involved in blood coagulation but not related to Vitamin-K dependent plasma proteins were inside the normal limits.

The levels of Vitamin K-dependent plasma anticoagulant proteins were found to be normal for protein C and low for protein S and Free protein S compared to the lowest limit of our laboratory (59% and 56% vs 65% and 60% respectively). Plasma levels of antithrombin III were normal. PCR amplification for FV (Leiden) and FII (G20210 A) mutation, gave negative results (normal genotype). It is worth mentioning, that the level of Vitamin K in our patient was below the lowest limits for Vitamin K in our laboratory.

COMMENT

Vitamin K is a fat-soluble vitamin. Because solubilization of fat must precede the absorption of vitamin K, all malabsorptive disorders, including a-betalipoproteinemia, may cause vitamin K deficiency. The liver is the major site of synthesis of fibrinogen, plasminogen and the vitamin K-dependent proteins. Vitamin K is required for the post-translational gamma-carboxylation of specific glutamyl residues in factors VII, IX, X, and II and proteins C and S[3-5].

In vitamin K-deficient states, levels of vitamin K-dependent plasma proteins are nearly normal, although the functions of these proteins in reactions that require a phospholipids surface are impaired. As vitamin K deficiency develops the activities of factor VII and protein C decreases, followed by diminished activities of factors IX, X and II. The body stores of vitamin K are relatively limited. A normal diet provides 300-500 μg of vitamin K, a very much larger amount than the normal requirement of 1 μg daily. Moreover, vitamin K, synthesized by the normal bowel bacteria, contributes to the daily requirements.

The results of this study concerning the Vitamin K-dependent factors involved in blood coagulation showed that: a) plasma levels of factor II (prothrombin) were almost identical to the lowest limit of our laboratory (69% vs 70%) {diagnosis of deficiency of this factor is suspected when both, PT and APTT (activated partial thromboplastin time) are prolonged and the thrombin time is normal}, b) the level of plasma factor VII was 37%, a percentage which is almost half the lower limit of normal values of our laboratory. However, no clinical manifestation of bleeding was described by the patient during the long history of the disease (diagnosis of factor VII deficiency should be considered if PT is prolonged while APTT is normal. In inherited disorders, levels of 10-20% of normal have been described), c) the levels of factor X was 43%, a value rather lower compared to the lowest limit of our laboratory (70%). (Deficiency of this factor is suspected when both PT and APTT are prolonged). However, the APTT value of our patient was normal. Finally, d) the level of factor IX was normal.

As far as the plasma Vitamin K-dependent anticoagulant proteins was concerned, the results of this study showed that, a) the levels of protein S and free protein S were 59% and 56% respectively, values that are close to the lower limit of our laboratory (65% and 60% respectively). It is well known that in some patients decreased levels of plasma protein S are associated with venous thrombosis, b) plasma protein C levels and levels of antithrombin III were normal. We know that the average concentration of antithrombin III in deficient patients is approximately 50% of normal and that the most frequent clinical manifestation of antithrombin deficiency is DVT (deep vein thrombosis)[6].

In conclusion, although the level of Vitamin K in patients with a,betalipoproteinemia is low due to fat malabsorption and, consequently, the levels of some Vitamin K-dependent plasma proteins are below the normal limits, no clinically significant consequences related to blood coagulation could be observed, even after many years of follow-up. However, we suggest that in patients with a, betalipoproteinemia, among other conservative measures, parenteral administration of Vitamin K is indicated, in order to correct PT and to improve the levels of some Vitamin K-dependent coagulation factors.

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