Inherited Vitamin K Deficiency: Case Report and Review of Literature

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Vitamin K is the cofactor for the hepatic carboxylation of glutamic acid residues in a number of proteins including the procoagulants factors II, VII, IX, and X. The role of vitamin K in normal bone function is not fully understood. Inherited deficiency of vitamin K dependent coagulation factors is a rare bleeding disorder reported only in a few patients. Here we present an 18-month old child who presented with osteopeni due to inherited vitamin K deficiency.

While the patient had high bone specific alkaline phosphatase and parathyroid hormone levels and low osteocalcin and bone mineral density values, with the regular supplementation of vitamin K all the mentioned parameters returned to normal values.

Key Words: Hereditary vitamin K deficiency, osteopenia, treatment, osteocalcin

INTRODUCTION

Vitamin K is a fat-soluble vitamin. It is a necessary cofactor for the hepatic carboxylation of glutamic acid residues in a number of proteins including the procoagulants factors II, VII, IX, and X. Vitamin K deficiency and treatment with vitamin K antagonists are two common acquired causes for decrease of vitamin K dependent coagulation factors. Acquired deficiency of vitamin K-dependent factors is common in newborns, in malabsorption and in biliary duct obstruction.[1] Inherited deficiency of vitamin K dependent coagulation factors is a rare bleeding disorder

reported only in a few patients according to our literature knowledge.

The role of vitamin K in normal bone function is not fully understood. However, osteocalcin has shown to be vitamin K-dependent.[1] Osteocalcin is synthesized by osteoblast, and it is known that carboxylated osteocalcin binds to the hydroxyapatite matrix of bone.[2] Osteocalcin is attracting attention as its importance in calcium homeostasis evolves.

We reported a case with inherited deficiency of vitamin K, which presented with osteopenia, and we also gave a brief literature review.

CASE REPORT

An 18-month-old male patient was admitted to the University Hospital, for evaluation of numerous haemorrhagic episodes with multiple bruises, but no hemarrthroses since birth. He had not taken antibiotics within several months of evaluation.

His parents were healthy. Although there was consanquinity (first cousins), no family history of another individual with abnormal hemorrhage was obtained.

Physical examination showed a well developed and nourished infant whose body measurements were normal for his age [height: 86 cm (75-90 centile), weight: 12000 gram (75-90 centile), head circumference: 48 cm (50 centile)]. On physical examination no skeletal abnormalities were noted. There was no historical or physical evidence of malabsorption or liver disease. Spesific tests for these disorders at the time of our initial studies

of hemostasis demonstrated normal values of serum transaminases, lactate dehydrogenase, bilirubin, total protein and albumin, gamma glutamyl transpeptidase, α_1-antitripsin, cholesterol, trigliseride, folate and vitamin B_{12}. There was no steatorrhea. Hematological examination showed anemia (9.8 g/dl) with hypochromia, anisocytosis, poikilocytosis on the peripheral smear. Ferritin level was low. White blood cell count and platelet counts were $9.1 \times 10^9/L$ and $31 \times 10^9/L$, respectively. Plain x-ray of the spine and palms were normal. The coagulation studies of our patient are shown in Table 1. The prothrombin time (PT) and activated partial thromboplastin time (aPTT) were prolonged. Clotting factors not dependent on vitamin K were normal throughout several determinations. No warfarin was detectable in the patient's plasma.

His parents and siblings had normal levels of PT, aPTT and factors II,VII, IX, X.

Total alkaline phosphatase (ALP) level was high (1157 IU/L) and bone-specific ALP level was 840 IU/L. Osteocalcin level was 5.5 ng/ml (normal range: 10-40 ng/ml). Calcium/creatinin in urine was 0.1. Bone mineral density (BMD) was evaluated by dual X-ray absorptiometry. BMD measurement at the AP spine (L1-L4) was 0.217 g/ cm^2. Parathyroid hormone (PTH) level was 233 pg/ml (normal range: 12-72 pg/ml).

On one occasion, parenteral administration of 10 mg vitamin K corrected PT to normal value and led to increase of factors II, VII, IX, X. However, PT and factors' levels returned to basal

values during the following weeks. Although we could not perform enzymatical analysis, we suggested that the patient had inherited vitamin K deficiency according to physical and laboratory examination (especially low osteocalcin level) and response to treatment (exacerbation of coagulation studies with discontinuation).

Although bone-specific ALP and PTH levels decreased, osteocalcin levels and BMD measurement gradually increased with vitamin K treatment [phytomenadione (Konakion MM paediatric®, Roche) 1 mg/week orally] (Table 2). Changes of osteocalcin, BMD and international normalized ratio (INR) measurement during the first year of treatment were shown in Fig. 1. During treatment PT, aPPT and vitamin K-dependent clotting factors were all normal (Table1).

DISCUSSION

Vitamin K-dependent proteins are present in a wide variety of tissues, including plasma (procoagulants - Factors II, VII, IX, X; anticoagulants - protein C and S; protein Z-function unknown), bone (osteocalcin or bone Gla-protein), kidney, lung, testes, spleen and placenta.[1] The best characterized are the vitamin K-dependent coagulation factors and osteocalcin. Osteocalcin is synthesized by osteoblasts. It is known that carboxylated osteocalcin binds to the hydroxyapatite matrix of bone.

Vitamin K after absorption, mediated by bile

Table 1. The Coagulation Test Results of the Patient

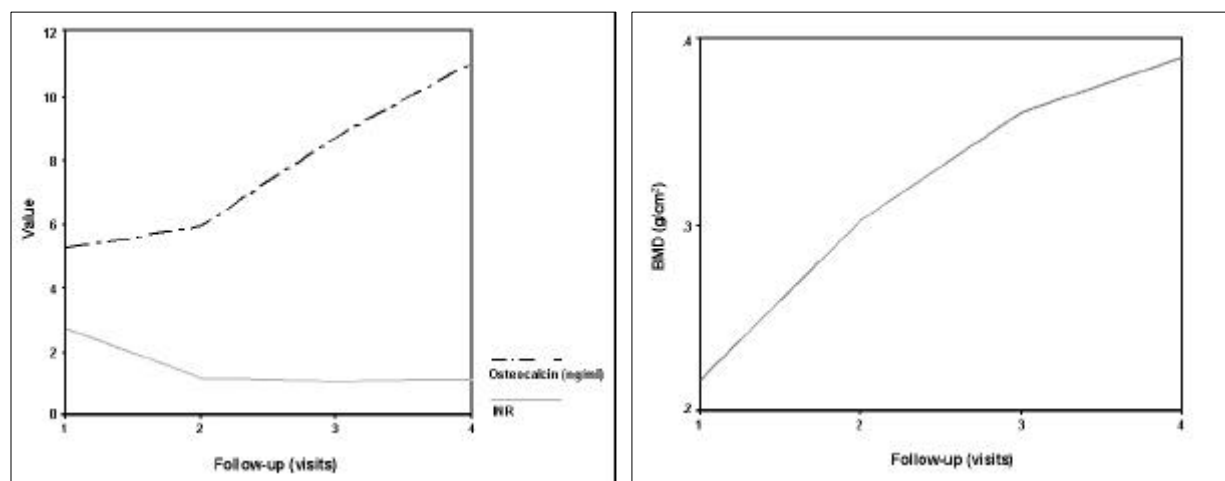| Factors	Before treatment	4th month of treatment	8th month of treatment	12th month of treatment
PT (s)	49.8	14.2	11.9	13.1
aPTT (s)	55.8	30.6	29.2	27.4
INR	2.7	1.16	1.05	1.11
Factor II (%)	4	43	56	75
Factor V (%)	100	100	-	-
Factor VII (%)	20	100	100	100
Factor VIII (%)	100	100	-	-
Factor IX (%)	7	100	100	96
Factor X (%)	2	60	65	90

Fig. 1. Graphical pattern of BMD, INR and osteocalcin levels during treatment.

Table 2. Bone-specific ALP, PTH, Osteocalcin Levels and BMD Measurements During the First Year of the Treatment

	Before treatment	4th month of treatment	8th month of treatment	12th month of treatment
Bone-specific ALP (IU/L)	840	694	638	330
PTH (pg/ml)	233	158	137	72
Osteocalcin (ng/ml)	5.5	6.2	8.7	11
BMD (g/cm^2)	0.217	0.302	0.36	0.386

and pancreatic lipases, is transported to the liver in chylomicrons and β-lipoproteins, where γ-carboxylation takes place; the system requires O_2, CO_2 and reduced vitamin K. In the process, vitamin K is metabolized to vitamin K-2,3-epoxide from which vitamin K is regenerated.[1,3] There is some evidence to support the view that vitamin K epoxide reductase and vitamin K quinone reductase activities are carried out by the same enzyme.[1] In its reduced form, vitamin K is a cofactor for the activation of the microsomal enzyme γ-glutamyl carboxylase, promoting the conversion of protein-bound glutamate residues (Glu) to γ-carboxyglutamate residues (Gla). The presence of Gla residues confers unique physiologic properties for calcium-mediated binding to negatively charged phospholipid surfaces. This is requirement for effective hemostasis. In the absence of vitamin K these precursor proteins are functionally inactive and circulate in their decarboxylated form (PIVKA: protein induced by vitamin K absence).[1] Defective vitamin K recy-

cling, e.g. with deficiencies of reductase, or a defect of the γ-carboxylase should all lead to an impaired γ-carboxylation and diminished activity of the vitamin K dependent proteins, including proteins C and S, and possibly of other vitamin K dependent proteins (e.g. osteocalcin and Gla-matrix protein) present in almost all tissue.[4] If vitamin K is depleted, Gla residues are not formed.[5]

Three bone-matrix noncollagenous proteins, matrix Gla protein, osteocalcin, and protein S, are posttranslationally modified by the action of vitamin K-dependent γ-carboxylases.[2] Osteocalcin is bone Gla protein that contains three γ-carboxyglutamate residues and binds to hydroxyapatite; and its expression correlates with mineralization. It regulates bone mineralization by both inhibiting mineral nucleation and stimulating osteoclast differentiation and activity. In contrast, matrix Gla protein contains five γ-carboxyglutamate residues that is not coupled to matrix mineralization[6]. Protein S is made primarily in the liver but also made by osteogenic cells. Protein S deficiency

may result in osteopenia.[2] Biosynthesis of the vitamin K-dependent proteins occurs in two steps. First, a polypeptide chain is produced on the ribosomes of the hepatocytes, a step that does not require the presence of the vitamin. Then a second carboxyl group is inserted into the gamma carbon of certain glutamic acid residues in the polypeptide chain by the action of the membrane-bound enzyme called carboxylase. Vitamin K is an essential cofactor for this reaction.[2] The propeptide of the vitamin K-dependent proteins contains a specific signal that appears to bind to carboxylase and to direct to formation of Gla residues. During the carboxylation reaction, vitamin K metabolized to vitamin K epoxide, which is then reduced back to vitamin K by the microsomal enzyme vitamin K epoxide reductase.[3,5]

Patients with prolonged PT and APPT and normal thrombin time have inherited functional deficiencies (fibrinogen, prothrombin, factor V or X; rarely inherited deficiency in several or even all the vitamin K-dependent cogulation factors) or acquired functional deficiencies, such as vitamin K deficiency, acute intravascular coagulation-fibrinolysis syndrome (reduced factors V and VIII and thrombocytopenia, increased fibrin[-ogen] split products), or liver disease (reduced vitamin K-dependent factors and factor V, increased factor VIII).[7] The diagnosis of vitamin K deficiency can be confirmed if normalization occurs after administration of a therapeutic dose of vitamin K is followed by a fall in the PT.[1] In the presence of normal absorption, oral vitamin K is effective, although correction of the PT is slower than following parenteral administration.[1]

Our patient did not demonstrate skeletal abnormalities. An adequate vitamin K status is necessary for early skeletal development. Interference with its synthesis in the fetus may play a role in the embriopathy induced by maternal ingestion of warfarin.[5] Some skeletal changes in a child with congenital deficiency of vitamin K epoxide reductase were reported.[8] This may related to effect on bone Gla proteins. Possible explanation for the defect in our patient is an alteration in the region of the carboxylase.

In our case, historical, clinical and laboratory presentation and response to oral vitamin K administration suggested inherited deficiency of

vitamin K although serum vitamin K concentration, enzyme analysis and potential mutations in the gamma-glutamyl carboxylase gene could not be identified. Hereditary deficiency of vitamin K-dependent coagulation factors due to defective carboxylase in Devon Rex cats can be normalized by vitamin K supplementation.[9] This finding may provide insight for the therapeutic effect of vitamin K in patients with γ-glutamyl carboxylase deficiency.

In a previous study, it was shown that administration of oral vitamin K2 significantly increased bone mineral density in severely handicapped patients complicated by osteopenia.[10] Koshihara, et al,[11] documented that vitamin K1 and K2, but not vitamin K3 enhanced in vitro mineralization when cells were cultured with vitamin K. In another study, osteocalcin-deficient mice were reported to have increased BMD compared with controls.[12] Although bone-specific ALP and PTH levels decreased, osteocalcin levels and BMD measurement gradually increased with vitamin K treatment in our patient. There is not sufficient literature knowledge about how osteocalcin levels changed in patients with vitamin K deficiency with treatment.

Increase in serum osteocalcin concentration reflects bone formation and is closely related to skeletal mineralization in osteopenia associated with vitamin K deficiency. Serial measurements of osteocalcin as a noninvasive approach to the follow-up of osteopenia may be indicator of successful therapy for clinician.

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