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Hereditary Deficiency of Vitamin K-Dependent Coagulation Factors With Skeletal Abnormalities

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We describe a female infant who presented with severe intracranial bleeding and was found to have a hereditary deficiency of vitamin K-dependent coagulation factors. She also had mild stippling of the left femoral epiphysis and shortness of the distal phalanges of the fingers. We studied the possible relationship between these abnormalities and a peroxisomal defect and followed their responses to treatment with vitamin K. The level of vitamin K-dependent clotting factors returned to near-normal following treatment with pharmacological doses of vitamin K, but there was no effect on the skeletal abnormalities. © 1996 Wiley-Liss, Inc.

KEY WORDS: vitamin K, clotting factors, coagulopathy, chondrodysplasia punctata, pseudowarfarin embryopathy

INTRODUCTION

Hereditary deficiency of vitamin K-dependent coagulation factors is a rare inborn error of metabolism, presumed to be due to a defect in the carboxylation of glutamic residues of vitamin K-dependent procoagulants and anticoagulants [Gallop et al., 1980; Brenner et al., 1990]. The mode of inheritance is thought to be autosomal recessive, but family studies are rare because most cases are sporadic. So far, fewer than a dozen patients have been reported, showing variability in the severity of coagulopathy. Skeletal abnormalities have been reported in only 2 patients [Pauli et al., 1987; Leonard, 1988]. We present a third patient (first female patient) with skeletal abnormalities. This report confirms previous reports and provides further delineation of the syndrome of coagulopathy and skeletal abnormalities, resembling warfarin embryopathy.

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CLINICAL REPORT

A 4-month old girl was hospitalized for vomiting and apathy beginning one day before admission. During a previous hospitalization a bulging fontanelle and respiratory insufficiency were noted, necessitating intubation and ventilation. She was thought to have bacterial meningitis and was referred to our hospital.

She was born after a normal 37-week pregnancy and delivery. Her previous history was unremarkable, except for congenital dislocation of the hip, which was treated conservatively. The parents are first cousins. The family history was unremarkable. Three other sibs are healthy. On admission, she was pale, hypothermic, and apathetic, and in severe respiratory distress. Her pulse was 160 per min. Blood pressure was not measurable. She bled at all puncture sites. Mid-facial hypoplasia was noted, with slight flatness of the nasal bridge. Fingers seemed to be somewhat shorter than normal. The nutritional status was good, and there were no signs of malabsorption. The rest of the physical findings were unremarkable.

Hemoglobin concentration was 1.7 gm%; there were 28,000 leukocytes and 60,000 platelets per mm^3. Prothrombin time was 14% and partial thromboplastin time 180 sec. Blood gases were normal, as were the plasma electrolytes and liver and kidney function. Plasma urea was 7.9 mM and the LDH level was 2,113 units. CSF was clear, with no cells found. A diagnosis of neonatal sepsis and disseminated intravascular coagulopathy was made.

She was treated with packed blood cells, repeated units of fresh frozen plasma, and antibiotics, and her hemodynamic and hematological condition stabilized. Treatment with phenytoin was started because of convulsions, but changed to phenobarbitone later. On the third day of hospitalization, the patient was still stuporous, the anterior fontanel was bulging, and there were signs of right hemiparesis. All cultures were sterile. A brain CT-scan showed a large area of ischemia of the left hemisphere with signs of bleeding and deviation of the midline. Thereafter, she gradually awakened, and her general status improved. She was discharged with right hemiparesis and right facial paresis. She was readmitted 3 days later because of pallor and apathy. A massive left subdural hematoma was

found on brain CT-scan. Burr holes were done and the patient was treated with fresh frozen plasma and cryoprecipitate. A detailed survey of the clotting system showed deficiency of vitamin-K-dependent clotting factors II (8%), VII (22%), IX (28%), and X (15%). These findings explain why both the prothrombin time (factors II, VII, and X deficiency) and partial thromoboplastin time (Factors II, IX, and X deficiency) were abnormal. The levels of factor V and factor XIII were normal (98% and 83%, respectively). There was no clinical indication of fat malabsorption and fat-soluble vitamins malabsorption. Results of liver function tests were normal. Treatment consisting of intramuscular injections of vitamin K and physiotherapy was started. After 7 days of treatment, factor II level was 60%, factor VII was 65%, factor IX was 112%, and factor X was 56%. Prothrombin time was 68% of control and partial thromboplastin time was 32 sec.

She was discharged on vitamin K injections (0.5 mg/kg body weight) every other day, phenobarbitone, and physiotherapy. Vitamin K was later given orally at a dose of 5 mg/kg body weight every other day, and changed thereafter to 10 mg/day. It should be noted that the prothrombin time and partial thromboplastin time never reached normal levels, compared with control values. On follow-up examinations (24 months) her psychomotor development is normal, with almost normal function of the right arm. No bleeding has occurred since the beginning of treatment. A controlled attempt to stop vitamin K treatment elicited a rapid decline in prothrombin and partial thromboplastin time.

Prothrombin and partial thromboplastin time were within normal limits in the plasma of both parents and other 3 sibs. Roentgenographic examination at 4 months showed mild stippling of the nucleus of the head of the left femur, and shortness of the distal phalanges of the fingers on all 4 limbs. The finding of short distal phalanges did not change significantly after a one-year treatment with vitamin K (Fig. 1). By contrast, the stippling of the head of the left femur disappeared (Fig. 2). However, as can be seen in Figure 2, the femoral capital epiphysis is smaller and slightly irregular. Irregularity is also noted in the middle and left third of the acetabulum. These findings may be due to subclinical hemarthrosis of the joint.

DISCUSSION

Hereditary deficiency of vitamin K-dependent coagulation factors is a rare metabolic disorder that seems to comprise variable phenotypic presentations. The primary biochemical defect in this disease is thought to be abnormal carboxylation of glutamic residues of vitamin K-dependent procoagulants and anticoagulants [Gallop et al., 1980; Brenner et al., 1990]. Swanson and Suttie [1985] suggested that the abnormal carboxylation was due to abnormal liver microsomal vitamin K carboxylase. In one patient [Pauli et al., 1987], inborn deficiency of vitamin K-epoxide reductase was shown. This warfarin inhibitable enzyme is responsible for the transformation of vitamin K to its active form [Pauli, 1988].

Skeletal abnormalities have been reported in only 2 cases. Pauli et al. [1987] reported increased irregularity and mild stippling of the perilumbar and perisacral region on roentgenographs taken on the first day of life

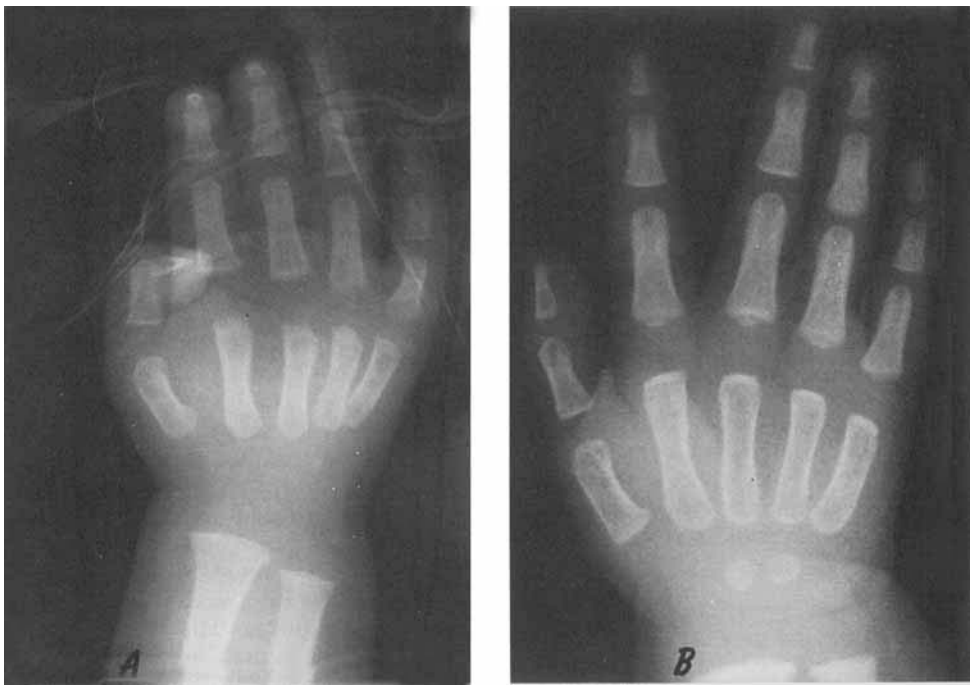

Fig. 1. Radiographs of the right hand at age 4 months **(A)**and at 16 months **(B).** Note short distal phalanges on both radiographs.

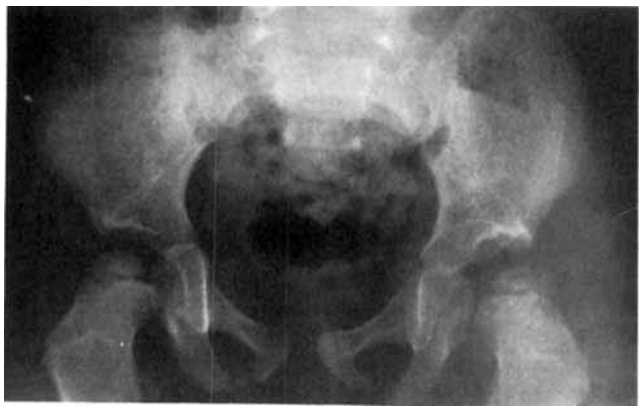

Fig. 2. Radiograph of the hip joints at age 16 months. Note irregularity of the left femoral capital epiphysis and of the acetabulum.

of their patient. There was also marked hypoplasia of the distal phalanges of all fingers. At the age of 7 9/12 years, there was no evidence of irregularity and stippling but the distal phalanges remained hypoplastic. The possibility that the patient might have had a concomitant mild form of chondrodysplasia punctata was considered, but the authors concluded that these findings are more likely to be due to the demonstrated enzyme defect [Pauli et al., 1987]. Furthermore, in view of the resemblance of these findings to those of warfarin embryopathy [Shaul et al., 1975], the authors also suggested a possible mechanism of teratogenicity of this medication and inhibition of post-translational carboxylation of osteocalcin was suggested [Pauli et al., 1976]. A similar patient has been evaluated by Leonard [1988]. Several characteristics of our patient, namely mid-face hypoplasia and flatness of the forehead and nasal bridge, as well as her roentgenographic findings at the age of 4 months, were remarkably similar to the previously reported cases [Pauli et al., 1987; Pauli, 1988; Leonard, 1988]. We examined the possibility of a concomitant chondrodysplasia punctata due to a peroxisomal disorder in our patient, as suggested in the first report of this syndrome [Pauli et al., 1987]. Peroxisomal activity, assessed by measuring both the activity of the peroxisomal enzyme dihydroxyacetonephosphate acyl transferase and the plasma level of very long chain fatty acids, was normal.

As mentioned above, the mode of inheritance of this syndrome is thought to be autosomal recessive. In all reported cases, including our patient, new X-linked dominant or recessive mutations causing chondrodysplasia are not likely. Mild chondrodysplasia punctata (Conradi-Hünerman syndrome) is an autosomal dominant defect. A new dominant mutation in our patient is possible but not very likely. Thus, the combination of coagulopathy, facial anomalies and skeletal abnormalities may represent a distinct syndrome, in which an impaired vitamin K-dependent γ-carboxylation of both coagulation factors and bone carboxylated proteins is probably the pathogenetic mechanism [Pauli et al., 1987; Pauli, 1988; Howe and Webster, 1994].

Our patient responded to vitamin K treatment by partial recovery of clotting factors synthesis, but her prothrombin time and partial thromboplastin time never exceeded 80% of normal, like those of the patient reported by Brenner et al. [1990]. Two patients reported by Goldsmith et al. [1982], who exhibited a mild or moderate defect which presented at a later age, responded to treatment with full recovery. Thus,it seems that the biochemical response to treatment is dependent on the severity of the defect.

CONCLUSIONS

The rarity of the skeletal findings and the lack of response of the bony abnormalities to treatment as opposed to the variable response of the hematological abnormalities, suggest that this rare inborn error of metabolism is a heterogenous disorder, as previously suggested by Brenner et al. [1990]. Whether the skeletal abnormalities represent one end of a spectrum of severity of the disease or indicate a different disorder with a different biochemical basis is not clear yet.

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