Bile Acid deficiency as cause of VKCFD in a Newborn

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Introduction

Vitamin K-hydroquinone functions as a cofactor for the endoplasmatic enzyme gamma-carboxylase (GGCX), which catalyses the posttranslational modification of glutamate residues into gamma-carboxy glutamate residues (Gla). Gla residues are essential for the function of coagulation factor II, VII, IX, and X. This process in turn generates vitamin-K-epoxide as a by-product. Subsequent reduction of vitamin-K-epoxide to the quinone form and further to the hydroquinone form by VKORC1 completes a recycling mechanism known as the vitamin K cycle. Combined deficiency of these factors (VKCFD) nowadays mostly is caused by defects in either GGCX or VKORC1 and represents a very rare autosomal recessive disorder.

In the past, postpartal vitamin K deficiency due to the limited placental permeability for vitamin K was a frequent cause of hypocoagulability and subsequent intracranial haemorrhage. Since introduction of vitamin K prophylaxis in newborn, spontaneous intracranial haemorrhages resulting from postpartal vitamin K deficiency decreased by more than 95%, but still is present in infants.

Case Report

Here we report a 3-month-old male infant suffering from spontaneous fever (39,5 C) since two days, recurrent vomiting, and paleness. Laboratory investigations showed Quick < 10 %, aPTT > 200 sek, and vitamin K dependent coagulation factor activity < 5%. X-ray computed tomography (CT) revealed an acute subdural haematoma and intracerebral haemorrhage. He was administered of vitamin K (1µg/kg i.v.) resulting in Quick > 40 % after 90 min. After additional administration of PPSB concentrate Quick normalized to 100 %. Due to continuous decrease of Quick over the next two days, vitamin K was substituted once a week resulting in normalized coagulation factor activity.

As no obvious signs of cholestasis were observed (bilirubin 0.3 mg/dl, normal value < 1.3 mg/dl), genetic analysis of VKORC1 and GGCX, the enzymes responsible for vitamin K recycling and gamma carboxylation, was initiated, but did not reveal any mutation. Therefore, we took a closer look on bile acids. Here, high serum levels of bile acids (241 µmol/l, normal value < 8 µmol/l) combined with low fat soluble vitamins but regular bilirubin and liver enzymes were diagnosed. Absence of phytosterols in serum confirmed malabsorption disease.

Vitamin K	FII	FVII	FIX	FX	Quick
without	< 5 %	< 5 %	< 5 %	-	< 10 %
1 µg / kg i.v.	30 %	48 %	60 %	34 %	43 %
2 mg / day p.o.	-	-	-	-	110 %

Vitamin	A [µg/dl]	1,25 D [ng/l]	E [µg/dl]
without substitution	13.5	38.0	23.0
with substituted bile acids (p.o.)	23.2	73.0	269
normal values	20-43	45-270	130-490

Conclusion

Since introduction of vitamin K prophylaxis, intracranial hemorrhage in infancy has decreased from ~ 34 per 100.000 to less than a tenth of this number. Although vitamin K-prophylaxis routinely is applied, in some cases vitamin K-deficiency can be considered as causation of intracranial bleeding in newborn. Often defects in the vitamin K cycle due to mutations in VKORC1 or GGCX resulting in VKCFD1 or VKCFD2 can be diagnosed. In rare cases, malabsorption of fat soluble vitamins including vitamin K can be seen. Therefore, measurement of serum bile acids and fat soluble vitamins should be considered in infants with vitamin K deficiency bleeding.

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