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Original article

Enteral nutrition and antibiotic use increase the risk for vitamin K deficiency in patients with severe motor and intellectual disabilities

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SUMMARY

Background & aims: We have investigated the possible risk factors for vitamin K deficiency in subjects with severe motor and intellectual disabilities (SMID).
Methods: Eighty-two SMID patients were evaluated for their vitamin K intake, serum PIVKA (protein induced by vitamin K absence) -II and ucOC (undercarboxylated osteocalcin) levels; which are vitamin K-dependent hepatic and bone markers, respectively.
Results: Thirty-six and 19 patients were receiving enteral nutrition (EN) and antibiotics, respectively. Although their serum levels were above the upper reference range in 52% of the subjects for PIVKA-II and 30% of those for ucOC, overt abnormalities in blood coagulation were not observed. Multivariate analyses revealed that EN and antibiotic treatment were significant predictors of the serum PIVKA-II and ucOC levels. Antibiotic treatment affected their serum levels differently in those with EN and those with oral intake (OI). In subjects without antibiotic treatment, vitamin K intake was significantly correlated with circulating levels of PIVKA-II and ucOC, and the breakpoints of vitamin K intake for PIVKA-II and ucOC were 2.5 μg/BW/day and 5.5 μg/BW/day, respectively.
Conclusions: Vitamin K deficiency was highly prevalent in SMID patients, especially in those receiving both EN and antibiotics. Considering the facts that much more vitamin K is required in the bone than in the liver, and the SMID patients are at high risk of fracture, vitamin K supplementation would be of help in these subjects.

1. Introduction

Severe motor and intellectual disabilities (SMID) or neurodevelopmental disabilities is a term proposed in 1996 that refers to patients with severe physical and mental retardation. Most SMID patients are bedridden or remain in a sitting position, and are characterized by an intelligence quotient (IQ) lower than 35. SMID is a legal term, the diagnosis of which is made based on the criteria defined in the Children's Welfare Act. Therefore, SMID includes various diseases that occur during the prenatal period, the neonatal period, and the first 18 years of life. Neurological abnormalities associated with multiple comorbidities constitute the fundamental pathophysiology of SMID patients, and are closely related to its treatment. For example, most patients with neurodevelopmental disabilities have dysphagia, which necessitates enteral feeding.[1,2] SMID patients, with diminished food intake, are likely to have a deficiency in their micronutrients status, which may have important clinical implications.

Vitamin K is essential in maintaining normal blood coagulation. In four of the coagulation factors (II, VII, IX, and X), the glutamyl (Glu) residue is converted to a γ-carboxyglutamyl (Gla) residue catalyzed by γ-carboxylase, which uses vitamin K as a co-enzyme. This conversion allows these coagulation factors to acquire the ability to bind calcium ion, and leads to their activation.[3] Therefore,

Abbreviations: SMID, severe motor and intellectual disabilities; ucOC, undercarboxylated osteocalcin; PIVKA-II, protein induced by vitamin K absence-II; CP, cerebral palsy; OI, oral intake; EN, enteral nutrition; AEDs, anti-epileptic drugs.

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a bleeding tendency is the classic symptom of vitamin K deficiency. There are also proteins that are vitamin K-dependently γ-carboxylated in tissues other than the liver, and many of these may have functional significance. Recently, vitamin K deficiency in extra-hepatic tissues has also been reported to be associated with health problems.[4,5]

Osteocalcin is a vitamin K-dependent Gla protein, and is the most abundant non-collagenous bone matrix protein produced by osteoblasts. Through γ-carboxylation, osteocalcin gains the ability to bind hydroxyapatite, and regulates bone mineralization.[4] Recent clinical evidences strongly suggest that skeletal vitamin K deficiency increases the risk of fractures.[6] Matrix Gla protein (MGP); another vitamin K-dependent protein, is an inhibitor of vascular calcification.[7,8] Therefore, vitamin K deficiency is associated with health problems in a tissue-specific manner, and thus leads to a bleeding tendency, osteoporosis, and vascular calcification due to vitamin K deficiency in the liver, skeleton, and vasculature, respectively.

Previous studies have indicated that the bleeding tendency is a serious clinical problem in SMID patients.[9] Additionally, subjects with neurodevelopmental disabilities are reported to be at a high risk of fractures.[10,11] Nevertheless, reports on the incidence of vitamin K deficiency in these patients are scarce.[12] These considerations led us to examine the vitamin K status in patients with SMID.

2. Subjects and methods

2.1. Subjects

The study subjects were 82 SMID patients (41 males and 41 females) living in the residential hospital, the Biwako Gakuen Kusatsu Medical and Welfare Center for Children and Persons with SMID. Detailed information about this study was provided to the subjects or their proxy, and written consent was obtained for their participation in this study. The study protocol was approved by the ethics committee of the institution described above. The exclusion criteria were treatment with vitamin K, warfarin, or multivitamin supplementation. Patients with pre-existing liver or bone disease were also excluded.

Of the 102 subjects residing in the above facility, written informed consent was obtained from 85 cases. Three subjects were excluded because they were taking vitamin K or warfarin. None of the subjects had experienced overt signs or symptoms attributable to vitamin K deficiency. In addition, none of the subjects were being treated with any drugs that may have interfered with the vitamin K metabolism. Mechanical ventilation support and tracheostomy were required in 7 and 18 subjects, respectively.

2.2. Biochemical measurements

Blood was obtained from each patient after an overnight fasting. After centrifugation, the serum was maintained at −30 °C until the analysis. The serum levels of protein induced by vitamin K absence-II (PIVKA-II) and undercarboxylated osteocalcin (ucOC) were measured by an electro chemiluminescence immunoassay (ECLIA) (EIDIA Co., Ltd, Tokyo, Japan), which are vitamin K-dependent hepatic and bone markers, respectively. In the current study, the reference range for PIVKA-II was defined to be less than 28 mAU/mL, which is 2SD above the mean value of 14.2 mAU/mL.[13] Similarly, the reference range for ucOC was 5.37 ng/mL for women, and 5.47 ng/mL for men, respectively, which are 2SD above the corresponding mean values (2.51 ng/mL for men and 3.01 ng/mL for women).[14] The platelet count and international normalized ratio (INR), were also measured. The laboratory reference range was 0.90–1.14.

2.3. Assessment of the nutrients intake

The 7-day nutrient intake was assessed by the food record method. The intake of vitamin K was calculated by multiplying the amount of vitamin K supplied from the institution by the average percentage intake. Based on these records, the intake of vitamin K by the patients was calculated using a software program (Healthy Maker Pro 501, Mushroom Software Corp, Okayama, Japan). The vitamin K intake/kg body weight was also calculated.[15]

2.4. Statistical analyses

Statistical analyses were performed using the SPSS 18.0 J software program for Windows (SPSS, Japan Inc., Tokyo, Japan). The associations between the variables were analyzed by the Spearman's correlation coefficient. The multiple regression analyses were performed to identify the independent variables that affect the vitamin K status. The differences between four independent groups were analyzed by the Mann–Whitney *U* test with the Bonferroni correction. The breakpoint for vitamin K intake was decided as follows. Subjects were divided into two groups; those with their vitamin K intake (μg/BW kg/day) above the predetermined cut-off value and those below it. Various cut-off values were screened starting from 1.0 μg/BW kg/day to 6.0 μg/BW kg/day with 0.5 μg/BW kg/day intervals. Then, comparison was made between the two groups on the serum concentrations of PIVKA-II and ucOC. The breakpoint was so determined as the cut-off level of vitamin K intake with the most significant difference, which was defined as the minimum *p* value or maximum absolute *t* value in Student's *t*-test.[16]

3. Results

3.1. The baseline patient characteristics and data from blood examinations

The baseline characteristics of the study subjects and the data from blood examination are shown in Table 1. Because of their

Table 1
Characteristics of subjects.

	Number/data	Duration (y)	Reference range
Bedridden state	63 (77)	38 ± 12 (37)	
Enteral feeding	36 (44)	16 ± 11 (14.5)	
Long-term antibiotic treatment	19 (23)	6.3 ± 3.9 (7.0)	
AED administration	71 (87)	36 ± 14 (35)	
Monotherapy	21 (26)	41 ± 14 (43)	
Combined therapy	50 (61)	34 ± 13 (33)	
Age (y)	39.4 ± 12.6 (39.0)		
Male/female	41/41		
Height (cm)	147.6 ± 10.5 (148.5)		
Weight (kg)	34.4 ± 5.6 (34.4)		
BMI (kg/m^2)	15.8 ± 2.2 (15.7)		
INR	1.02 ± 0.10 (1.01)		0.90–1.14
Serum albumin (g/dL)	4.0 ± 0.4 (4.0)		3.7–5.3
Serum total cholesterol (mg/dL)	166 ± 29 (164)		130–219
Serum triglyceride (mg/dL)	80 ± 39 (71)		35–149
Cholinesterase	307 (256, 360)		200–465
GOT (U/L)	22 (18, 28)		10–40
GPT (U/L)	19 (14, 24)		6–40
γGTP (U/L)	57 (32, 94)		<48
Creatinine	0.40 ± 0.13 (0.42)		M0.6–1.15/ F0.45–0.85
C-reactive protein	0.29 (0.13, 1.00)		<0.30

Mean ± SD (Med), Median (Q1–Q3).