นิพนธ์ต้นฉบับ

ภาวะขาดวิตามินที่ละลายในไขมันในกลุ่มผู้ป่วยเด็กโรคท่อน้ำดีตีบตันหลังผ่าตัดระบายน้ำดีลงสู่ลำไส้

กรกนก ศรีมนัส, นฤมล ตนะทิพย์, อลิสรา ดำรงมณี, ณัฐพงษ์ อัครผล
ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

Received March 27, 2024 Revised May 26, 2024 Accepted June 25, 2024

บทคัดย่อ

ความเป็นมา: การขาดวิตามินที่ละลายในไขมันเป็นหนึ่งในภาวะแทรกซ้อนที่พบได้ในผู้ป่วยเด็กโรคท่อน้ำดีตีบตัน แม้ปัจจุบันจะมีแนวทางเสริมวิตามินและการให้โภชนบำบัดในผู้ป่วยกลุ่มนี้แล้ว แต่ก็พบว่าผู้ป่วยส่วนใหญ่ยังคงมีอาการและอาการแสดงของภาวะทุพโภชนาการและการขาดวิตามิน หากไม่ได้รับการรักษาที่เพียงพอภาวะนี้อาจเป็นอุปสรรคและส่งผลกระทบต่อผู้ป่วยรวมถึงผลลัพธ์ของการปลูกถ่ายตับในอนาคต

วัตถุประสงค์: เพื่อศึกษาความชุกของภาวะขาดวิตามินที่ละลายในไขมันในกลุ่มผู้ป่วยเด็กโรคท่อน้ำดีตีบตันหลังผ่าตัดระบายน้ำดีลงสู่ลำไส้ และมีวัตถุประสงค์รองเพื่อหาปัจจัยเสี่ยงที่สัมพันธ์กับภาวะขาดวิตามินที่ละลายในไขมันในกลุ่มผู้ป่วยดังกล่าว

วิธีการศึกษา: ตรวจวัดระดับวิตามินที่ละลายในไขมันในผู้ป่วย โดยถือว่าผู้ป่วยมีการขาดวิตามินที่ละลายในไขมันเมื่อมีข้อใดข้อหนึ่งต่อไปนี้ 1) วิตามินเอน้อยกว่า 0.7 ไมโครโมล/ล. 2) ระดับ 25-OH D น้อยกว่า 20 นาโนกรัม/มล. 3) อัตราส่วนระหว่างวิตามินอีต่อคอเลสเตอรอลน้อยกว่า 2.22 ไมโครโมล/มิลลิโมล 4) ค่า INR มากกว่า 1.5 และสามารถแก้ไขได้ด้วยการให้วิตามินเค

ผลการศึกษา: ผู้ป่วยทั้งสิ้น 30 ราย เป็นชาย 13 ราย และหญิง 17 ราย อายุเฉลี่ย 7.9 ปี พบความชุกของการขาดวิตามินที่ละลายในไขมันอย่างน้อย 1 ชนิดถึงร้อยละ 36.7 (95% CI 18.4, 54.9) โดยมีภาวะขาดวิตามินเอร้อยละ 36.7 รองลงมาคือวิตามินดี วิตามินอี และวิตามินเคตามลำดับ จากการวิเคราะห์ข้อมูลแบบตัวแปรเดียว พบว่าการขาดวิตามินที่ละลายในไขมันในประชากรกลุ่มที่ศึกษามีความสัมพันธ์กับผู้ป่วยที่มีการผ่าตัด Kasai ที่ล้มเหลว ภาวะตับโต ผลตรวจทางห้องปฏิบัติการมีระดับ total bilirubin, direct bilirubin, PELD score และ inflammatory markers (ESR, CRP) สูง มีภาวะซีด โดยมีระดับ BUN และ Cr ในเลือดต่ำกว่ากลุ่มที่ไม่พบว่ามีภาวะขาดวิตามินที่ละลายในไขมัน

สรุป: การขาดวิตามินที่ละลายในไขมันในผู้ป่วยท่อน้ำดีตีบตันยังเป็นปัญหาที่พบได้บ่อย โดยพบการขาดวิตามินเอมากที่สุด ดังนั้น การติดตามระดับวิตามินอย่างใกล้ชิด จึงเป็นสิ่งสำคัญที่ช่วยป้องกันและปรับการรักษา โดยเฉพาะในผู้ป่วยที่มีค่า PELD score ที่สูง และมีแนวโน้มที่จะได้รับการรักษาโดยการผ่าตัดเปลี่ยนตับในอนาคต

คำสำคัญ: ท่อน้ำดีตีบตัน เด็ก โภชนาการ วิตามินที่ละลายในไขมัน ขาดวิตามิน

Prevalence of fat-soluble vitamins deficiency in patients with post hepaticoportoenterostomy biliary atresia

Kornkanok Srimanus, Narumon Tanatip, Alisara Damrongmanee, Nuthapong Ukarapol

Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Thailand

Abstract

Background: One of the under-recognized complications in children with extrahepatic biliary atresia (EHBA) is fat-soluble vitamins (FSV) deficiency, which if left untreated, inevitably compromises long-term clinical outcomes, including liver transplantation (LT).

Objectives: To primarily evaluate the prevalence of fat-soluble vitamins (FSV) deficiency in children with EHBA. The secondary objective was to explore any possible associated risk factors.

Methods: The data were collected from patients diagnosed with EHBA who underwent hepaticoportoenter ostomy (HPE) via a cross-sectional study conducted from February 2022 to June 2023. FSV deficiency was diagnosed if there was one of the followings: 1) vitamin A level < 0.7 micromol/L, 2) serum 25-OH D < 20 ng/mL, 3) vitamin E to cholesterol ratio < 2.22 micromol/mmol, or 4) INR > 1.5 correctable with parenteral vitamin K administration. The prevalence of FSV deficiency was presented as frequency and percentage.

Results: Thirty EHBA patients (13 males) with an average age of 7.9 years old were consecutively enrolled. The prevalence of at least one FSV deficiency was 36.7% (95% CI 18.4, 54.9), in which the most common one was vitamin A deficiency (36.7%), followed by the deficiency of vitamin D, E, and K, respectively. Univariate analysis showed statistically significant differences in success rate of Kasai's operation, hepatomegaly, albumin, total bilirubin, direct bilirubin, hemoglobin level, anemia for ages, ESR, CRP, BUN, creatinine level, and PELD score between those with and without any FSV deficiency.

Conclusion: Vitamin A deficiency was the most frequently observed. Adequate vitamin supplementation should be carefully reviewed to prevent its deficiency, particularly in EHBA patients with high PELD scores, potentially indicative of LT.

Keywords: biliary atresia, child, nutrition, fat-soluble vitamins, deficiency

Introduction

Neonatal jaundice caused by extrahepatic biliary atresia (EHBA) is one of the most critical cholestatic conditions which urgently requires surgical correction and proper management to prevent progressive hepatic fibrosis, cirrhosis, and eventually liver failure. Its pathogenesis remains unclear. Genetic mutation, biliary tract/vascular malformation, infections, and toxin exposure have been investigated as possible causes of the disease.[1] Kasai's hepaticoportoenterostomy (HPE) has still been accepted as a curative treatment, although its outcomes are variable and dependent on several factors. Patients with unfavorable surgical outcomes experience progressive chronic liver disease, portal hypertension, variceal bleeding, cholangitis, fat malabsorption, and fat-soluble vitamins deficiency.[2-5] These complications, if inappropriately treated, can affect post-liver transplant (LT) outcomes. Inadequate supplementation of fat-soluble vitamins can impair immune functions, epithelial regeneration, bone composition, neurological development, and liver coagulation factors synthesis, leading to increased susceptibility to infections, fractures, neuromuscular diseases, bleeding, etc.

Although there have been established nutritional guidelines for infants with cholestasis, protein-energy malnutrition, and fat-soluble vitamins deficiency have still been continuously reported. Dong, et al. reported 15.3%, 8.5%, and 3.6% of patients with biliary atresia developed at least one fat-soluble vitamins deficiency after Kasai's operation at one, three, and six months, respectively.[6] Patients with high AST, ALT, ALP, GGT, and total bilirubin tended to compromise fat-soluble vitamins absorption. This comprehensive information would help physicians provide appropriate and individualized nutritional adjustments.

Objectives

This study primarily aimed to determine the prevalence of fat-soluble vitamins deficiency in pediatric patients with EHBA after HPE at Chiang Mai University (CMU) Hospital. Exploring potential clinical risk factors was a secondary objective outcome.

Method

All biliary atresia patients younger than 15 years old in outpatient setting who underwent Kasai's operation were asked for written informed consent and consecutively enrolled in this cross-sectional study from February 2022 to June 2023. The initial sample size estimation of 49 subjects, based on the prevalence of previous studies[6,7], was calculated. The patients were excluded from the study if having 1) a recent infection or critical illness within four weeks at the enrollment, 2) liver transplantation, and 3)

co-morbidities, including enteropathy, renal diseases, endocrine disorders, and coagulopathy from hematologic conditions. Demographic information, medical history, current medications, dietary history, and estimated daily sunlight exposure time were systematically reviewed from the medical records and history taking. Physical examination was performed focusing on clinical signs of fat-soluble vitamins deficiency. Besides basic laboratory data, fat-soluble vitamins levels were assessed, in which vitamin A and E levels were measured by high-performance liquid chromatography (HPCL) using a 1260 Infinity II LC system (Agilent, USA), whereas the serum vitamin D (25OH-D) level was analyzed by electrochemiluminescence immunoassay (ECLIA) method using the Cobas e411 analyzer (Roche, Switzerland). Vitamin K status was indirectly assessed by INR level measured by Turbidimetric/Coagulometric measurements by ACL TOP500 analyzer. Uncorrectable INR with parenteral vitamin K administration was defined as poor hepatic synthetic function and/or liver failure, otherwise, it would be secondarily considered as malabsorption. Fat-soluble vitamins deficiency was diagnosed if if there was one of the followings: 1) vitamin A level < 0.7 micromol/L, 2) serum 25-OH D < 20 ng/mL, 3) vitamin E to cholesterol ratio < 2.22 micromol/mmol, or 4) INR > 1.5 which was normalized after parenteral vitamin K administration. For the statistical analysis, the qualitative data would be descripted and presented as frequency/percentage, whereas the quantitative data will be summarized either as median (IQR) or mean (SD). Further comparative analyses with either Chi's square or an appropriate non-parametric test using a $p < 0.05$ was carried out to determine any feasible associated factors. The study protocol (code: PED-2564-08631) was approved by the Research Ethics Committee of the Faculty of Medicine, Chiang Mai University.

Results

Thirty EHBA patients (13 males) with an average age of 7.9 years old were enrolled in the study. Mean (±SD) age of surgery is 86.6 (± 40.9) days. Eighty percent of the patients had successful Kasai's operation, based on clearance of jaundice after 3 months of the surgery.[8] Of those, 83.3% experienced cholangitis with a mean number of cholangitis episodes of 3.9. Other complications related to the underlying disease including GI bleeding, fracture, steatorrhea, ascites, and non-GI hemorrhage were observed in 20, 13.3, 6.7, 6.7, and 6.7%, respectively. The anthropometric study showed underweight and stunting in six children, whereas two had low mid-upper arm circumference by age. During the study period, merely 40, 56.7, 26.7, and 3.3% of the cases were being supplemented with vitamins A, D, E, and parenteral vitamin K, respectively. The baseline demographic and clinical characteristics were shown in Table 1.

Table 1 Demographic, medical history, and relevant physical examination data (N = 30)

Parameter	N = 30	
General demographic parameter		
Age (month, mean ± SD)	94.5	±49.3
Age of surgery (day, mean ± SD)	86.6	± 40.9
Duration after Kasai's operation (month, median (IQR))	94.4	50.2-137.9
Sex (male) (n, %)	13	43.33
Nutritional history and parameter	n	%
Exclusive BF > 6 months	14	46.7
MCT-containing formula supplementation	2	6.7
Adequacy of milk consumption (>480 ml/day)	25	83.3
Adequacy of sunlight exposure (>15 min/day)	24	80.0
Receiving vitamin A supplementation	12	40.0
Daily dose of vitamin A supplementation (IU/day, mean ± SD)	2,833	± 1,154
Receiving vitamin D supplementation	17	56.7
Daily dose of vitamin D supplementation (IU/day, mean ± SD)	4,321	± 3,101
Receiving vitamin E supplementation	8	26.7
Daily dose of vitamin E supplementation (IU/kg/day, mean ± SD)	15.52	± 10.51
**Periodically receiving vitamin K supplementation, parenteral route	1	3.3
History of illnesses	n	%
History of GI bleeding	6	20.0
***History of bleeding at other sites	2	6.7
History of steatorrhea	2	6.7
History of cholangitis	25	83.3
Number of cholangitis (n = 25, mean ± SD)	3.9	± 3.4
History of fracture	4	13.3
Abnormal physical examination	n	%
Hepatomegaly	21	70.0
Splenomegaly	17	56.7
Ascites	2	6.7
Clubbing of fingers	12	40.0

Abnormal physical examination (ต่อ)	n	%
Fracture from physical examination	1	3.3
Signs of vitamin A deficiency (keratomalacia and Bitot's spot)	0	0.0
Hyperreflexia	3	10.0
Cerebellar signs	0	0.0

*The recorded patients had received medium-chain triglycerides (MCT) containing formula during the study period.

**Depending on INR level at each visit

*** Intracerebral hemorrhage and hematoma on cheeks

Regarding FSV status, we found that vitamin A was the most vulnerable nutrient to become deficient compared to the others. This study demonstrated vitamin A deficiency in 36.7%, followed by vitamin D, E, and K deficiency in 6.7, 6.7, and 3.3% of the study population, respectively. Overall, the prevalence of at least one FSV deficiency was 36.7% (95% CI 18.4, 54.9). Apart from FSV, we also investigated the prevalence of iron and vitamin C deficiency, which were 33.3% and 27.3%, respectively. Eight of 30 had anemia for age, of which five and three were associated with iron deficiency and chronic disease, respectively. In the failed Kasai's operation group, 83.3% exhibited at least one FSV deficiency, whereas in the successful group, only 20.8% had at least one FSV deficiency. Laboratory data and primary study outcomes were shown in Table 2.

Table 2 Laboratory data and primary outcomes (N = 30)

Parameter	Median	IQR
Hb (g/dL)	12.5	(10.9, 13.3)
Hct (%)	36.9	(34.2, 39.7)
Platelet count ($x10^9$/L)	123	(83, 217)
TSAT (%)	24.2	(14.9, 32.3)
TSAT<16% (n, %)	10	33.3
Ferritin (mcg/L)	65	(23, 118)
Anemia (n, %)	8	26.7
Iron deficiency anemia (n, %)	5	16.7
Anemia of chronic disease (n, %)	3	10.0

Parameter	Median	IQR
INR	1.03	(0.96, 1.1)
PTT (s)	36.4	(34.1, 39.1)
Albumin (g/dL)	4.1	(3.6, 4.4)
Globulin (g/dL)	3.2	(2.7, 3.7)
Alkaline phosphatase (IU/L)	373.5	(279, 524)
AST (IU/L)	75.5	(37, 120)
ALT (IU/L)	50.5	(26, 82)
Total bilirubin (mg/dL)	1.3	(0.6, 2.6)
Direct bilirubin (mg/dL)	0.6	(0.3, 1.9)
GGT (IU/L, median (IQR))	95.5	(42, 230)
Nutritional deficiency status	n	% (95% CI)
Iron deficiency	10	33.3 (15.4, 51.2)
Vitamin A deficiency (< 0.7 mcmol/L)	11	36.7 (18.4, 54.9)
Vitamin D deficiency (25OH vitamin D < 20 ng/mL)	2	6.7 (0, 16.1)
Vitamin E deficiency by level definition (< 10 mcmol/L)	1	3.3 (0, 10.1)
Vitamin E deficiency by ratio definition (< 2.22)	2	6.7 (0, 16.1)
Vitamin E deficiency (Summary)	2	6.7 (0, 16.1)
Vitamin K deficiency (INR > 1.5, correctable w/ vitamin K)	1	3.3 (0, 10.1)
At least 1 fat soluble vitamin deficiency	11	36.7 (18.4, 54.9)
*Vitamin C deficiency (<11 mcmol/L)	6	27.3 (7.1, 47.5)

* n =22

After applying Chi-square and Mann-Whitney U tests for univariate analysis, significant risks that compromised the FSV status were identified including the presence of hepatomegaly and anemia, lower albumin, hemoglobin, BUN and Cr levels, and higher total bilirubin, direct bilirubin, ESR, CRP, and PELD score (Table 3).[9] Figure 1 clearly showed a significantly higher TB and DB level in EHBA patients having at least one FSV deficiency compared to those without. Unfortunately, when applying multivariate analysis, none of these factors was found to contribute to the risk of FSV deficiency in our population.

Table 3 Risk analysis for any FSV deficiency in EHBA children (univariate analysis)

Parameter	Any FSV def. (n = 11)	No FSV (n = 19)	p value
Clinical parameter			
Age (mo), median (IQR)	79.2 (22.6, 141.9)	98.8 (66.3, 133.4)	0.561
Age <5 y, 9 (30%)	5 (55.6%)	4 (44.4%)	0.161
Age at HPE, median (IQR)	67 (34, 104)	90 (79, 113)	0.089
Successful Kasai's operation, 24 (80%)	6 (25%)	18 (75%)	0.008
Underweight (weight <P3), 6 (20%)	3 (50%)	3 (50%)	0.380
Stunting (height <P3), 6 (20%)	3 (50%)	3 (50%)	0.380
MUAC (< P3), 2 (6.7%)	2 (100%)	0	0.126
Hepatomegaly, 21 (70%)	11 (52.3%)	10 (47.6%)	0.006
Splenomegaly, 17 (56.6%)	7 (41.2%)	10 (58.8%)	0.558
History of GI bleeding, 6 (20%)	4 (66.7%)	2 (33.3%)	0.088
Ascites, 2 (6.7%)	1 (50%)	1 (50%)	0.607
Steatorrhea, 2 (6.7%)	2 (100%)	0 (0%)	0.126
History of cholangitis, 25 (83.3%)	9 (36%)	16 (64%)	0.865
Number of cholangitis, median (IQR)	3 (1, 5)	2 (1, 5)	0.446
Laboratory parameter			
Albumin g/dL, median (IQR)	3.6 (3.2, 3.8)	4.4 (4, 4.7)	<0.001
AST IU/L, median (IQR)	105 (60, 241)	69 (36, 117)	0.106
ALT IU/L, median (IQR)	63 (40, 82)	43 (21, 72)	0.245
TB mg/dL, median (IQR)	2.59 (1.52, 6.32)	0.73 (0.46, 1.88)	0.002
DB mg/dL, median (IQR)	1.96 (1.08, 5.94)	0.34 (0.22, 0.81)	0.001
GGT IU/L, median (IQR)	149 (63, 238)	87 (32, 218)	0.355
Hb g/dL, median (IQR)	10.8 (10.5, 12.1)	12.7 (12.2, 13.3)	0.010
TSAT %, median (IQR)	25.35 (13.68, 31.21)	23.08 (14.99, 33.22)	0.451
Ferritin microgram/L, median (IQR)	118 (23, 164)	35 (22, 78)	0.138
Anemia for age, 8 (26.7%)	6 (75%)	2 (25%)	0.028
ESR mm/h, median (IQR)	24 (10, 53)	6.5 (5, 9)	0.006
Elevated CRP > 5 mg/L, 5 (16.7%)	5 (100%)	0	0.003
BUN mg/dL, median (IQR)	7 (6, 10)	10 (7, 12)	0.034

Laboratory parameter (ต่อ)

Cr mg/dL, median (IQR)	0.28 (0.19, 0.34)	0.35 (0.29, 0.43)	0.035
Other parameters			
UDCA treatment, 26 (86.7%)	11 (42.3%)	15 (57.7%)	0.102
PELD score, mean (SD)	4.25 (8.4)	0.95 (3.78)	0.030

MUAC: mid-upper arm circumference, AST: aspartate transferase, ALT: alanine transaminase, TB: total bilirubin, DB: direct bilirubin, GGT: gamma-glutamyl transferase, Hb: hemoglobin, TSAT: transferrin saturation, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, BUN: blood urea nitrogen, Cr: creatinine, UDCA: ursodeoxycholic acid, PELD: pediatric end-stage liver disease

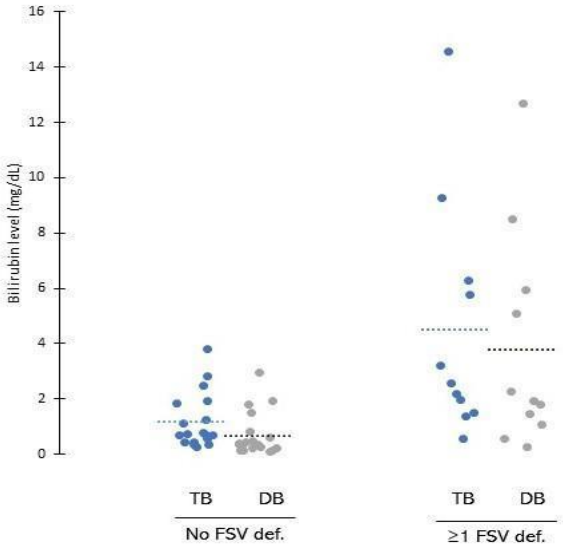

Figure 1 Total and direct bilirubin levels in EHBV children with and without FSV deficiency

Discussion

In patients with EHBA, malnutrition, particularly FSV insufficiency has seldom been a top priority of attention, when compared to more serious complications such as esophageal variceal bleeding, hepatopulmonary syndrome, portopulmonary hypertension, massive ascites, and liver failure. This study surveyed the prevalence of FSV deficiency among EHBA Thai children at CMU hospital, the magnitude of which was undoubtedly high and should not be ignored. The overall prevalence of at least one FSV deficiency was 36.7% (95%CI 18.4, 54.9), in which vitamin A was the most common FSV deficiency, followed by vitamin D, E, and K, respectively. Even among successful Kasai's operation patients, the prevalence of FSV deficiency remained at 25%. Apart from FSV, we also found that our study population had a high prevalence of iron (33.3%) and vitamin C (27.3%) deficiency. The results were consistent with

previous reports from urban and rural areas in Thailand, where iron deficiency remained the most common nutritional problem in children, followed by vitamin D and vitamin A deficiency.[10] These may partly be explained by lower storage of iron and vitamin A in younger children accompanied by relatively rapid cellular growth and differentiation compared to adults.[11] Compared to other FSV, the prevalence of vitamin K deficiency in this study is relatively low, this may be attributed to the selected method of measurement, using INR instead of vitamin K level, in which the later could be more sensitive in detecting early vitamin K deficiency. A cohort study from China reported incidence of one or more deficiencies of vitamin A, D, or E in biliary atresia children at two weeks, 1, 3, and 6 months after HPE of 27.8, 15.2, 8.5, and 3.6%, respectively. Although there was an improvement trend, vitamin A, like ours, is the most compromising nutrient, with 6.8% of BA children showing its deficiency.[6] However, there was a relatively high incidence of at least one FSV insufficiency in BA children of 58, 53, and 57% at one, three, and six months after HPE was reported in a US study.[7] Although it is not possible to directly compare the results from any part of the world due to different methodology, demographic, and geographic distribution, this silent but significant problem should not be ignored, especially in the era of liver transplantation, in which nutritional status is one of the outcome determinations.

Besides the well-known roles of FSV in health, several studies have recently shown that the degree of vitamin D insufficiency is associated with the severity of liver fibrosis. A decrease in an inhibitory signal on the TGF-beta/SMAD-dependent transcriptional response of pro-fibrotic gene in the hepatic stellate cells has been postulated as a pathogenesis link.[12-14] An animal model study also showed that *vdr* $^{-/-}$ mice developed more bile duct injury by losing bile duct epithelial polarity after bile duct ligation compared to the wild-type strains.[15] Moreover, a clinical observational study demonstrated a negative correlation between vitamin D levels and NAFLD fibrotic score.[16] Therefore, the role of vitamin D could be far beyond muscle and bone.

Regarding risk evaluation, only univariate analysis could be performed in this study due to the limited sample size. In alignment with previous reports,[6,7] EHBA children with high bilirubin levels in accordance with failed Kasai's operation tended to be at risk for the development of FSV insufficiency. Shneider et al.[7] showed that infants with BA having TB > 2 mg/dL are at risk for FSV deficiency. Venkat et al.[17] also found negative correlations between TB and vitamin A, D, and E levels. This finding was further supported by our study, in which all 11 EHBA children with TB < 2 mg/dL, not receiving FSV supplementation, did not have biochemical evidence of any FSV deficiency. Elevated total and direct bilirubin levels could result in increased fat malabsorption, thereby leading to a higher prevalence of FSV deficiency. We also observed significant lower levels of BUN and creatinine in the FSV deficiency group,

demonstrating the association between surrogate nutritional and FSV deficiency status. Additionally, serum albumin level as a negative acute phase reactant and parameter for the nutritional status tended to be lower in children with FSV deficiency. Serum albumin levels, in composite with total bilirubin, results in the PELD score becoming a comprehensive risk factor for FSV insufficiency in EHBA patients.

Interestingly, the increase in inflammatory surrogate markers, including ESR and CRP was also associated with the risk for FSV deficiency. Silva et al.[18] demonstrated that serum retinol levels were inversely associated with CRP levels. The study also showed a positive and significant association between CRP level and hepcidin level, in which hepcidin, a protein synthesized by the liver, decreases iron absorption in the duodenum. Its genetic (*HAMP* gene) expression is enhanced by vitamin A deficiency.[19] As a nutrient having anti-inflammatory properties and growth factors for erythrocyte progenitors, vitamin A deficiency could be a potential risk factor for EHBA children for anemia of chronic disease as well as iron deficiency. Moreover, a high prevalence of vitamin C deficiency could contribute to poor iron absorption in this population. Apart from those mentioned earlier, active forms of vitamin D were able to decrease *HAMP* expression demonstrated in treated cultured hepatocytes and monocytes.[20] This experiment highlighted the role of vitamin D supplements in CKD patients presenting with anemia, which could be potentially applied in EHBA children as well.

Unfortunately, only 30 patients in our center met the inclusion criteria and agreed to participate in the study period, which does not reach the numbers of sample size estimation for prevalence study, leading to less precised prediction of the prevalence rate with a wide range of 95%CI. Additionally, this definitely reduced statistical power to determine associated risks, in particular applying multivariate analysis.

Conclusion

In summary, the prevalence of FSV deficiency is not uncommon in EHBA patients. Among them, vitamin A insufficiency was the most frequently observed, which was consistent with malnutrition in children reported all over the world. Adequate vitamin supplementation should be carefully reviewed to prevent its deficiency, particularly in EHBA patients with high PELD scores, potentially indicative of LT.

Acknowledgements

Funding: This work was supported by the Faculty of Medicine Research Fund, Chiang Mai University, Grant No. 101-2565.

References

1. Sanchez-Valle A, Kassira N, Varela VC, Radu SC, Paidas C, Kirby RS. Biliary Atresia: Epidemiology, genetics, clinical update, and public health perspective. Adv Pediatr. 2017;64:285-305.
2. Peng CH, Lee HC, Jiang CB, Hsu CK, Yeung CY, Chan WT, et al. Serum vitamin D level is inversely associated with liver fibrosis in post Kasai's portoenterostomy biliary atresia patients living with native liver. PLoS One. 2019;14:e0218896.
3. Tazawa Y, Nakagawa M, Yamada M, Konno T, Tada K, Ohi R, et al. Serum vitamin E levels in children with corrected biliary atresia. Am J Clin Nutr. 1984;40:246-50.
4. Yanofsky RA, Jackson VG, Lilly JR, Stellin G, Klingensmith WC, 3rd, Hathaway WE. The multiple coagulopathies of biliary atresia. Am J Hematol. 1984;16:171-80.
5. Ng J, Paul A, Wright N, Hadzic N, Davenport M. Vitamin D levels in infants with biliary atresia: Pre- and post-Kasai portoenterostomy. J Pediatr Gastroenterol Nutr. 2016;62:746-50.
6. Dong R, Sun S, Liu XZ, Shen Z, Chen G, Zheng S. Fat-soluble vitamin deficiency in pediatric patients with biliary atresia. Gastroenterol Res Pract. 2017;2017:7496860.
7. Shneider BL, Magee JC, Bezerra JA, Haber B, Karpen SJ, Raghunathan T, et al. Efficacy of fat-soluble vitamin supplementation in infants with biliary atresia. Pediatrics. 2012;130:e607-14.
8. Tamgal J, Damrongmanee A, Khorana J, Tepmalai K, Ukarapol N. Clearance of jaundice after the modified Kasai;s operation predicts survival outcomes in patients with biliary atresia. Turk J Pediatr. 2019;61:7-12.
9. McDiarmid SV, Anand R, Lindblad AS, Principal I, Institutions of the Studies of Pediatric Liver Transplantation Research G. Development of a pediatric end-stage liver disease score to predict poor outcome in children awaiting liver transplantation. Transplantation. 2002;74:173-81.
10. Rojroongwasinkul N, Kijboonchoo K, Wimonpeerapattana W, Purttiponthanee S, Yamborisut U, Boonpraderm A, et al. SEANUTS: The nutritional status and dietary intakes of 0.5-12-year-old Thai children. Br J Nutr. 2013;110:S36-44.
11. Saron ML, Godoy HT, Hessel G. Nutritional status of patients with biliary atresia and autoimmune hepatitis related to serum levels of vitamins A, D and E. Arq Gastroenterol. 2009;46:62-8.

12. Udomsinprasert W, Jittikoon J. Vitamin D and liver fibrosis: Molecular mechanisms and clinical studies. Biomed Pharmacother. 2019;109:1351-60.
13. Zhuang P, Sun S, Dong R, Chen G, Huang Y, Zheng S. Associations between vitamin D and liver function and liver fibrosis in patients with biliary atresia. Gastroenterol Res Pract. 2019:4621372.
14. Ko BJ, Kim YS, Kim SG, Park JH, Lee SH, Jeong SW, et al. Relationship between 25-hydroxyvitamin D levels and liver fibrosis as assessed by transient elastography in patients with chronic liver disease. Gut Liver. 2016;10:818-25.
15. Firrincieli D, Zuniga S, Rey C, Wendum D, Lasnier E, Rainteau D, et al. Vitamin D nuclear receptor deficiency promotes cholestatic liver injury by disruption of biliary epithelial cell junctions in mice. Hepatology. 2013;58:1401-12.
16. Kim HS, Rotundo L, Kothari N, Kim SH, Pyrsopoulos N. Vitamin D is associated with severity and mortality of non-alcoholic fatty liver disease: A US population-based study. J Clin Transl Hepatol. 2017;5:185-92.
17. Venkat VL, Shneider BL, Magee JC, Turmelle Y, Arnon R, Bezerra JA, et al. Total serum bilirubin predicts fat-soluble vitamin deficiency better than serum bile acids in infants with biliary atresia. J Pediatr Gastroenterol Nutr. 2014;59:702-7.
18. Silva AP, Pereira ADS, Simoes BFT, Omena J, Cople-Rodrigues CDS, de Castro IRR, et al. Association of vitamin A with anemia and serum hepcidin levels in children aged 6 to 59 mo. Nutrition. 2021;91-92:111463.
19. Gutowska K, Formanowicz D, Formanowicz P. Interrelations between iron and vitamin A-studied using systems approach. Int J Mol Sci. 2022;23:1189.
20. Bacchetta J, Zaritsky JJ, Sea JL, Chun RF, Lisse TS, Zavala K, et al. Suppression of iron-regulatory hepcidin by vitamin D. J Am Soc Nephrol. 2014;25:564-72.