Turkish Journal of Pediatric Disease

Original Article

The role of essential fatty acid deficiencies in cognitive function among patients with organic acidemias

Enes Kaan Kılıç[1], Özlem Ünal Uzun[2], Kaan Çelebier[1], Ayberk Selek[3], Çağatay Uğur[4], Metin Yiğit[1], Furkan Kalaycı[1], Aynur Küçükçongar Yavaş[5], Mehmet Gündüz[5]

[1]Department of Pediatrics, Ankara Bilkent City Hospital, Ankara, Türkiye, [2]Department of Nutrition and Metabolism, Kocaeli University, Kocaeli, Türkiye, [3]Department of Child Neurology, Hacettepe University, Ankara, Türkiye, [4]Private Practice, Ministry of Health Licensed, Cagatay Ugur Clinic, Ankara, Türkiye, [5]Department of Nutrition and Metabolism, Ankara Bilkent City Hospital, Ankara, Türkiye

Corresponding Author: **Enes Kaan Kılıç** e-mail: eneskaank@gmail.com

Received : 28.01.2026, Accepted : 05.05.2026 DOI: 10.12956/TJPD.2025.1300

ABSTRACT

Objective: Organic acidemias (OAs) are metabolic disorders characterized by enzyme deficiencies that impair amino acid catabolism, leading to metabolic imbalances. Essential fatty acids (EFAs), particularly Omega-3 and Omega-6, are vital for cellular and neurological functions but are often affected by protein-restricted diets used in OA management. The aim of this study was to evaluate the plasma EFA levels in OA patients and explores their clinical relevance.

Materials and Methods: A prospective, case-control design was adopted, including 26 OA patients (methylmalonic acidemia, propionic acidemia, isovaleric acidemia, maple syrup urine disease) and 22 healthy age- and gender-matched controls. Plasma EFA levels were quantified via gas chromatography-mass spectrometry. Cognitive and psychiatric evaluations were performed using standardized tests, including DSM-V-TR criteria, Wechsler Intelligence Scale for Children, and other psychometric tools. Statistical analyses assessed the relationships between EFA levels and clinical findings.

Results: Organic acidemias patients exhibited significantly lower levels of docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) + DHA, and Omega-3 compared to controls, with higher Omega-6/Omega-3 ratios. Despite these findings, no significant correlations emerged between EFA levels and cognitive or psychiatric outcomes.

Conclusion: EFA deficiencies are prevalent among OA patients on protein-restricted diets, underscoring the potential need for targeted nutritional interventions. However, the absence of a direct association with clinical findings suggests multifactorial influences on disease outcomes. Future research should explore the longitudinal effects of EFA supplementation and its role in mitigating neurodevelopmental impairments in OA.

Keywords: Docosahexaenoic acid, essential fatty acids, metabolic disease, omega-3

Introduction

Organic acids are compounds with weak acidic properties that contain carbon skeletons. In patients diagnosed with organic acidemia, there is a deficiency in the enzymes responsible for amino acid catabolism. As a result, organic acids, which emerge as intermediate metabolites during physiological processes, accumulate and disrupt acid-base balance and intracellular biochemical and metabolic pathways. To date, many types of organic acidemia have been identified. The most common group involves disorders of branched-chain amino acid metabolism, including maple syrup urine disease (MSUD), methylmalonic acidemia (MMA), propionic acidemia (PA), and isovaleric acidemia (IVA). Other frequently seen types are biotin-unresponsive 3-methylcrotonyl-CoA carboxylase deficiency, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase deficiency, and ketothiolase deficiency (1).

The analysis of organic acids in urine is crucial for diagnosing organic acidemia. The diagnosis is confirmed through high-performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GC-MS), or tandem mass spectrometry, followed by enzyme and DNA analyses (2). A key principle of treatment is the rapid removal of toxic substrates and the early implementation of dietary therapy by restricting specific nutrients. This approach increases long-term survival and reduces complications. Patients

with organic acidemia must avoid not only animal-based foods but also some plant-based foods with high protein content. Severe protein restriction can be compensated by consuming specialized amino acid mixtures that lack critical amino acids. However, dietary protein restrictions may lead to reduced intake of amino acids, vitamins, trace elements, and polyunsaturated fatty acids (3).

Fatty acids are named according to the position of their first double bond from the terminal omega carbon, resulting in classifications such as Omega-3, Omega-6, Omega-7, and Omega-9. Essential fatty acids, which the body cannot synthesize and must be obtained from the diet, cause characteristic symptoms when deficient. While humans can produce saturated and monounsaturated fatty acids, they cannot generate the double bonds present in Omega-3 and Omega-6 fatty acids, making these two critical members of the essential fatty acid group (4).

This study aimed to determine the levels of essential fatty acids in patients with organic acidemia on protein-restricted diets and to evaluate the clinical significance of essential fatty acid deficiencies.

Materials and Methods

This study was designed as a prospective, cross-sectional case-control study. It included 26 patients diagnosed with organic acidemia (MMA, PA, IVA, MSUD) who had been followed for at least six months at the Metabolism and Nutrition Outpatient Clinic of the Ankara Pediatric Hematology Oncology Training and Research Hospital. All patients over six months old who applied between January 2018 and October 2018 were included in the study. Patients with cobalamin-related hyperhomocysteinemia were excluded. Informed consent was obtained from all participants.

During routine follow-up visits, patients were informed about the study, and their physical examinations were conducted by a metabolic specialist. Measurements, including head circumference, body weight, and height, were recorded and evaluated against standard growth curves. The findings from physical examinations were documented. On the same day, blood samples were taken for routine tests and serum lipid profiling. Blood samples for essential fatty acid analysis were collected in heparin tubes after at least three hours of fasting. A minimum of 3 cc of blood was collected, centrifuged, and stored at -80°C until analysis. For comparison, the control group included 23 healthy children of similar age and gender who were followed at the general outpatient clinic.

The specific amino acid mixtures provided to the patients were as follows:

- MMA and PA patients: OS-1® or OS-2®, containing restricted valine, isoleucine, methionine, and threonine.
- IVA patients: Leu-1® or Leu-2®, containing restricted leucine.
- MSUD patients: MSUD-1® or MSUD-2®, containing restricted valine, leucine, and isoleucine.

All samples from the patients and controls were analyzed together in a single batch. Essential fatty acid levels were measured using gas chromatography-mass spectrometry (GC-MS) following the SIM analysis method. Plasma samples underwent methylation and hydrolysis before being injected into the Shimadzu GCMS QP 2010SE device. The column oven temperature was gradually increased from 100°C to 220°C, with the helium gas flow set at 1 mL/min. Results were expressed as percentages.

On the same day as their physical examinations, the patients were evaluated by a child psychiatrist. If a same-day psychiatric evaluation was not feasible, it was conducted within 1–3 months during subsequent follow-up visits. Psychiatric evaluations were carried out in accordance with DSM-V-TR criteria (Diagnostic and Statistical Manual of Mental Disorders). Depending on the patients' age, screening tools or cognitive tests were administered. Cognitive assessments included: Ankara Developmental Screening Inventory (AGTE), Stanford-Binet Intelligence Test, and Wechsler Intelligence Scale for Children – Revised Version (WISC-IV) (5-7). For patients whose developmental and cognitive levels permitted, additional psychometric tests, such as the Stroop Test and Cancellation Test, were used to assess attention. IQ levels were classified as follows: Bright intelligence (IQ>120), Normal cognitive function (IQ 90–120), Borderline intelligence (IQ 80–90), Mild cognitive delay (IQ 70–80), Moderate cognitive delay (IQ 50–70), and Severe cognitive delay (IQ<50).

Statistical analysis:

All data were analyzed using IBM Statistical Package for the Social Sciences, version 20.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). The Mann-Whitney U test and Independent samples T test were used for comparing two independent groups by distribution type. For comparisons involving more than two groups, the Kruskal-Wallis one-way analysis of variance was used. Categorical data were analyzed using the Chi-square test. Relationships between quantitative variables were assessed using Spearman's rank correlation analysis. Descriptive statistics were expressed as mean and standard deviation (SD) for normally distributed variables and as median (minimum–maximum) for non-normally distributed variables. Categorical variables were expressed as frequencies and percentages. Statistical significance was set at $p < 0.050$.

Results

This study included 26 patients diagnosed with branched-chain amino acid metabolism disorders (MSUD, MMA, PA, IVA). Of these patients, nine (35%) had MSUD, seven (27%) had MMA, five (19%) had PA, and five (19%) had IVA. The ages of the patients ranged from four months to 24 years, with a mean age of 6.31±5.45 years (median; 5.34 years). Of the total patients, 17 (65.4%) were male, and nine (34.6%) were female. The age at diagnosis ranged from the neonatal period to eight years, with a median age of one month and a mean age of 1.01 ±2.18 years. The average total protein intake was 2.06±0.48 g/kg/day, while the natural protein intake averaged 0.87± 0.17 g/kg/day.

Psychiatric assessments were not performed on five of the patients. Among the remaining 21 patients, 14.3% (n=3)

Table I: Cognitive and psychiatric assessments of the patient group

	Values*
Cognitive Evaluation	
Normal intelligence	3 (14.3)
Borderline intelligence	3 (14.3)
Mild cognitive delay	8 (38.1)
Moderate cognitive delay	4 (19.0)
Severe cognitive delay	3 (14.3)
Psychiatric Diagnosis	
No diagnosis	5 (23.8)
Attention-Deficit/Hyperactivity Disorder (ADHD)	1 (4.8)
Specific learning disorder	1 (4.8)
Autism	1 (4.8)
Autism + Cognitive Delay	3 (14.3)
Cognitive Delay only	10 (47.6)

***:** *n (%)*

Table II: Serum lipid profiles of the patient group

Lipid Parameter	Values*
Total cholesterol (mg/dL)	143.04±39.34
Triglycerides (TG) (mg/dL)	107.92±52.08
HDL (mg/dL)	48.89±13.84
LDL (mg/dL)	71.88±32.21
VLDL (mg/dL)	21.49±10.87

***:** *mean±SD*

had normal cognitive function, while the majority (52.4%, n=11) were classified with borderline intelligence or mild cognitive delay. In 33% (n=7) of the patients, moderate to severe cognitive delay was observed. Table I summarizes the cognitive and psychiatric assessments of the patients.

Table II summarizes the serum lipid profiles of the patient group. The mean total cholesterol level was 143.04±39.34 mg/dL, indicating overall cholesterol values within a generally acceptable range. Triglyceride levels averaged 107.92± 52.08 mg/dL, showing moderate variability among patients. The mean HDL cholesterol level was 48.89±13.84 mg/dL, reflecting relatively favorable protective lipid levels, while LDL cholesterol averaged 71.88±32.21 mg/dL. Additionally, the mean VLDL level was 21.49±10.87 mg/dL. Overall, the lipid profile suggests a balanced lipid status in the patient group, with considerable interindividual variation.

No statistically significant differences were observed between groups for ALA and EPA levels (p=0.103 and p=0.062, respectively). However, DHA levels were markedly lower in the patient group compared with controls (p=0.001). While linoleic acid (LA), DGLA, and arachidonic acid (AA) levels were similar between groups, combined EPA+DHA and total omega-3 fatty acid levels were significantly reduced in patients (p=0.001). In contrast, omega-6 levels were significantly lower in the patient group (p=0.004), yet the omega-6/omega-3 ratio was dramatically higher among patients, indicating a pronounced imbalance favoring omega-6 fatty acids (p=0.004). Additionally, the AA/DHA ratio was significantly elevated in the patient group (p=0.005), whereas the AA/EPA ratio did not differ significantly between groups. Overall, DHA, EPA+DHA, Omega-3 and Omega-6 levels were significantly lower in the patient group compared

Table III: Comparison of essential fatty acid levels between patient and control groups

Fatty Acid	Control	Patient	p
Number of patients	22	26	-
ALA (%)*	0.10 (0.1-0.1)	0.10 (0-0.10)	0.103
EPA (%)*	0.10 (0.10-2.8)	0.10 (0-3.91)	0.062
DHA (%)*	2.36 (0.1-5.76)	0.10 (0-12.52)	0.001
LA (%) †	69.47±28.36	71.22±29.19	0.591
DGLA (%) †	2.44±0.98	2.68±3.00	0.373
AA (%) †	13.09±4.41	13.10±10.80	0.396
EPA+DHA (%) †	2.89±1.84	1.58±3.42	0.001
Omega-3 (% †)	2.98±1.83	1.67±3.42	0.001
Omega-6 (%) †	92.51±20.67	86.79±32.14	0.004
Omega 6/ Omega- 3 †	39.45±22.69	195.37±152.59	0.004
AA/EPA †	106.53±62.75	118.95±103.29	0.772
AA/DHA †	6.19±3.67	62.20±89.63	0.005

***:** *median (min-max) (Mann Whitney U test),* **†:** *mean±SD (Independent samples T test)*

to the control group. Conversely, Omega-6/Omega-3, and AA/DHA ratios were significantly higher in the patient group (Table III).

Table IV shows the relationship between cognitive levels and essential fatty acid profiles. Although mean EPA+DHA and total omega-3 levels were higher in the normal/borderline cognitive group compared with the mild and moderate–severe delay groups, these differences were not statistically significant (p=0.659). In contrast, omega-6 levels and the omega-6/omega-3 ratio tended to increase with lower cognitive impairment, but no significant associations were observed (p=0.659). The AA/EPA and AA/DHA ratios also showed a progressive increase from normal/borderline cognition to moderate–severe delay, suggesting a trend toward a more pro-inflammatory fatty acid profile with worsening cognitive status; however, these trends did not reach statistical significance (p=0.564 and p=0.343, respecively). Overall, while variations in fatty acid composition across cognitive levels were apparent, no significant relationships were identified in this analysis.

Discussion

There are only a limited number of studies in the literature comparing Omega-3 and Omega-6 levels in patients diagnosed with organic acidemia. In this study, we compared the ratios of Omega-3 and Omega-6 fatty acids between the patient and control groups. Our findings are consistent with the few similar studies in the literature. This study also included a larger number of patients compared to previous research. Cognitive function and neurodevelopment in individuals with organic acidemia may be affected not only by the primary disease but also by Omega-3 deficiency. For this reason, we evaluated both cognitive status and Omega-3/Omega-6 levels, but no significant correlation was found.

Sanjurjo et al. (8) compared five patients with MMA and eight with urea cycle defects—both on protein-restricted

Table IV: Relationship between cognitive levels and essential fatty acid levels

Fatty Acid	Normal / Borderline*	Mild Delay*	Moderate / Severe Delay*	p†
EPA+DHA (%)	4.61±6.42	0.80±0.89	0.85±1.14	0.659
Omega-3 (%)	4.69±6.40	0.90±0.89	0.95±1.14	0.659
Omega-6 (%)	95.31±6.40	99.10±0.89	99.05±1.14	0.659
Omega-6/Omega-3	180.13±168.30	219.64±142.11	248.54±143.12	0.659
AA/EPA	99.28±96.92	129.39±88.61	161.88±130.50	0.564
AA/DHA	36.44±37.29	51.74±63.71	103.58±138.00	0.343

**: mean±SD, †: Kruskal-Wallis*

diets—with a control group of 50 healthy individuals. In their study, the free plasma levels of arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) were found to be lower in the patient group. The only discrepancy with our study lies in the EPA levels, which were also low in our control group, possibly explaining this difference.

Vilaseca et al. (9) divided patients with metabolic disorders into two groups: those on protein-restricted diets and those not on such diets. The study included 63 patients (four with PA, five with MSUD, and nine with cobalamin deficiency) on restricted diets and 69 patients on unrestricted diets. Higher erythrocyte and plasma DHA levels were found in the group without dietary restrictions. Similarly, in our study, DHA levels were significantly lower in the patient group following a protein-restricted diet compared to the control group.

Mazer et al. (10) evaluated six female MSUD patients aged 12–30 years and compared their essential fatty acid levels with those of 12 healthy controls. They found lower DHA levels and higher alpha-linolenic acid (ALA) levels in the MSUD group, which is consistent with our findings. Vlaardingerbroek et al. (11) studied 33 patients with metabolic disorders, including 10 with branched-chain amino acid metabolism disorders, and compared them with 38 controls. In their study, DHA levels were lower in the patient group, which aligns with the results of our study.

Drecksen et al. (12) compared the essential fatty acid levels of 10 IVA patients with those of 53 healthy controls. They reported a decrease in all Omega-3 fatty acid levels and an increase in the Omega-6/Omega-3 ratio in the patient group. As emphasized by Simopoulos et al. (13), maintaining a proper balance between essential fatty acids is crucial for normal growth and development. Consistent with both Drecksen's and our study, the Omega-6/Omega-3 ratio was found to be elevated in the patient group.

Aldámiz-Echevarría et al. (14) conducted a study in which 4 patients with MMA received DHA supplementation. They compared the total cholesterol, HDL, triglyceride (TG), and essential fatty acid levels of these patients with those of control and placebo groups. At the start of the study, the mean levels of total cholesterol, HDL, and TG were 114.7 mg/dL, 48.5 mg/dL, and 144 mg/dL, respectively. No significant difference in essential fatty acid levels was observed between the groups at baseline. However, after DHA supplementation, DHA and Omega-3 levels increased significantly, while TG levels decreased. In our study, DHA and Omega-3 levels were significantly lower in the patient group compared to the control group. The average levels of total cholesterol, HDL, and TG in our study were 143 mg/dL, 48.9 mg/dL, and 108.89 mg/dL, respectively. Differences in essential fatty acid levels between studies may be due to variations in sample size and patient age. Additionally, the higher total cholesterol and lower TG levels in our study are noteworthy.

Barschak et al. (15) evaluated the biochemical parameters of seven MSUD patients and compared them with healthy controls. They found that total cholesterol levels were significantly higher in the control group, but no significant differences were observed in HDL, LDL, or TG levels. In our study, HDL, LDL, and TG levels were within normal reference ranges and were not compared with those of the control group.

No studies in the literature have directly explored the effects of essential fatty acid levels on cognitive development in individuals with organic acidemia. However, El-Ansary et al. (16) conducted an animal study in which rats were given propionic acid to induce neurotoxicity. They found that Omega-3 fatty acids increased the levels of GABA, serotonin, and dopamine in the brain, as well as the formation of phosphatidylserine, phosphatidylethanolamine, and phosphatidylcholine. Omega-3 fatty acids also protected the rats from propionic acid-induced neurotoxicity.

In phenylketonuria (PKU), another metabolic disorder requiring a protein-restricted diet, several studies have examined the effects of essential fatty acid supplementation on cognitive and neurological function. Koletzko et al. (17) administered DHA supplements to 36 children with PKU for three months and reported improvements in visual function, motor skills, and coordination, accompanied by increased plasma DHA and EPA levels and decreased arachidonic acid (AA) levels. Children underwent visual evoked potentials (VEP) testing before and after supplementation, and a subgroup was additionally assessed using the Rostock–Oseretzky Scale (ROS), with untreated age-matched controls showing no comparable improvements. Similarly, Agostoni et al. (18) conducted a double-blind study in 20 patients with hyperphenylalaninemia who received DHA and EPA supplementation for 12 months and observed improvements in visual function alongside increased DHA levels. In contrast, more recent randomized controlled trials in PKU have shown that although DHA supplementation dose-dependently increases plasma DHA levels, it does not consistently result in measurable improvements in cognitive

or neurological outcomes within the tested dose ranges (19). In line with these observations, our study conducted in children with organic acidemias found that mean EPA+DHA and total omega-3 levels tended to be higher in the normal/borderline cognitive group compared with the mild and moderate–severe delay groups; however, these differences did not reach statistical significance, limiting conclusions regarding a direct association. In comparison, randomized controlled trials in healthy school-aged children have indicated that regular consumption of oily fish, rather than isolated supplementation, may be associated with modest improvements in cognitive and socioemotional functioning, particularly in attention and cognitive flexibility, as well as reductions in parent-reported internalizing and overall difficulties (20). The presence of dose–response relationships with EPA+DHA status and the use of whole fish underscore the potential importance of combined nutritional effects during ongoing brain development, while also highlighting the need for further adequately powered studies across different metabolic conditions.

Limitations

Several limitations of this study should be acknowledged. First, only free plasma essential fatty acid levels were measured; fatty acid composition in erythrocyte membranes or phospholipid fractions, which may better reflect long-term fatty acid status, was not assessed. Second, the cross-sectional design limits causal inference between fatty acid levels and cognitive outcomes. Third, although this study includes one of the largest cohorts of patients with organic acidemias evaluated for essential fatty acid status to date, the sample size may still be insufficient to detect subtle associations with neurodevelopmental measures. Finally, the absence of reference data on essential fatty acid levels in healthy Turkish children limits population-specific comparisons. Despite these limitations, this study provides valuable insight into essential fatty acid profiles in organic acidemias and highlights important directions for future research.

Conclusion

The findings of this study are consistent with the limited existing literature on essential fatty acid profiles in patients with organic acidemias. Our results confirm that children with organic acidemias, particularly those on protein-restricted diets, exhibit lower omega-3 fatty acid levels and higher omega-6/omega-3 ratios compared with healthy controls. Although omega-3 fatty acids are known to play an important role in neurodevelopment, no significant association was identified between omega-3 or omega-6 levels and cognitive outcomes in the present cohort. This lack of association may reflect the multifactorial nature of neurodevelopment in organic acidemias, in which metabolic control, disease severity, dietary management, and genetic factors interact alongside fatty acid status. Future longitudinal and interventional studies with larger sample sizes are needed to better define the clinical relevance of essential fatty acid supplementation and to clarify its potential role in improving neurodevelopmental outcomes in this patient population.

Ethics committee approval
This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Pediatric Hematology Oncology Training and Research Hospital (25.12.2017 , reference number: 2017-137).

Contribution of the authors
Study conception and design: EKK, ÖÜU; data collection: KÇ, AS, ÇU,MY; analysis and interpretation of results: MY, FK, ÖÜU, EKK, AKY, MG; draft manuscript preparation: EKK, KÇ,MY,FK. All authors reviewed the results and approved the final version of the article.

Source of funding
The authors declare the study received no funding.

Conflict of interest
The authors declare that there is no conflict of interest.

References

1. Abdelkhalek ZS, Abdelbaky MA, Elmonem MA. The metabolomics of organic acidemias: current advances and future prospects. Metabolomics. 2025;21(5):1-12. https://doi.org/10.1007/s44162-025-00118-6
2. Phipps WS, Jones PM, Patel K. Amino and organic acid analysis: Essential tools in the diagnosis of inborn errors of metabolism. Adv Clin Chem. 2019;92:59-103. https://doi.org/10.1016/bs.acc.2019.04.001
3. Chapman KA. Practical management of organic acidemias. Translational Science of Rare Diseases. 2019;4(3-4):121-131. https://doi.org/10.3233/TRD-190039
4. Xu R, Molenaar AJ, Chen Z, Yuan Y. Mode and Mechanism of Action of Omega-3 and Omega-6 Unsaturated Fatty Acids in Chronic Diseases. Nutrients. 2025;17(9):1540. https://doi.org/10.3390/nu17091540
5. Savaşır I, Sezgin N and Erol N. Ankara Gelişim Tarama Envanteri El Kitabı. Ankara: Türk Psikologlar Derneği; 1994.
6. Uğurel-Şemin R, Stanford-Binet ölçeğinin İstanbul çocuklarına uygulanması: 1960'da yapılan üçüncü değişiklik hakkında el kitabı, L ve M formlarının bileşimi. İstanbul Üniversitesi Fen Fakültesi, İstanbul 1987
7. Öktem F, Erden G, Gençöz T, Sezgin N, Uluç, S. Wechsler Çocuklar için Zeka Ölçeği-IV (WÇZÖ-IV) Uygulama ve Puanlama El Kitabı Türkçe Sürümü. Ankara: Türk Psikologlar Derneği Yayınları. 2016;
8. Sanjurjo P, Ruiz JIR, Montalvo MM. Inborn errors of metabolism with a protein-restricted diet: Effect on polyunsaturated fatty acids. J Inherit Metab Dis. 1997;20(6):783-9. https://doi.org/10.1023/A:1005367701176
9. Vilaseca MA, Gómez-López L, Lambruschini N, Gutiérrez A, García R, Meavilla S, et al. Long-chain polyunsaturated fatty acid concentration in patients with inborn errors of metabolism. Nutr Hosp. 2011;26(1):128-36.
10. Mazer LM, Yi SH, Singh RH. Docosahexaenoic acid status in females of reproductive age with maple syrup urine disease. J Inherit Metab Dis. 2010;33(2):121-7. https://doi.org/10.1007/s10545-010-9066-x
11. Vlaardingerbroek H, Hornstra G, de Koning TJ, Smeitink JAM, Bakker HD, de Klerk HBC, et al. Essential polyunsaturated fatty acids in plasma and erythrocytes of children with inborn errors of amino acid metabolism. Mol Genet Metab. 2006;88(2):159-65. https://doi.org/10.1016/j.ymgme.2006.01.003
12. Dercksen M, Kulik W, Mienie LJ, Reinecke CJ, Wanders RJA, Duran M. Polyunsaturated fatty acid status in treated isovaleric acidemia patients. Eur J Clin Nutr. 2016;70(10):1123-6. https://doi.org/10.1038/ejcn.2016.95

13. Simopoulos AP. An increase in the omega-6/omega-3 fatty acid ratio increases the risk for obesity. Nutrients. 2016;8(3):128. https://doi.org/10.3390/nu8030128

14. Aldámiz-Echevarría L, Sanjurjo P, Elorz J, Prieto JA, Pérez C, Andrade F, et al. Effect of docosahexaenoic acid administration on plasma lipid profile and metabolic parameters of children with methylmalonic acidaemia. J Inherit Metab Dis. 2006;29(1):58-63. https://doi.org/10.1007/s10545-006-0182-6

15. Barschak AG, Marchesan C, Sitta A, Deon M, Giugliani R, Wajner M, et al. Maple syrup urine disease in treated patients: Biochemical and oxidative stress profiles. Clin Biochem. 2008;41(5-6):317-24. https://doi.org/10.1016/j.clinbiochem.2007.12.024

16. El-Ansary AK, Al-Daihan SK, El-Gezeery AR. On the protective effect of omega-3 against propionic acid-induced neurotoxicity in rat pups. Lipids Health Dis. 2011;10:142. https://doi.org/10.1186/1476-511X-10-142

17. Koletzko B, Beblo S, Demmelmair H, Müller-Felber W, Hanebutt FL. Does dietary DHA improve neural function in children? Observations in phenylketonuria. Prostaglandins Leukot Essent Fatty Acids. 2009;81(2-3):159-64. https://doi.org/10.1016/j.plefa.2009.05.001

18. Agostoni C, Scaglioni S, Bonvissuto M, Bruzzese MG, Giovannini M, Riva E. Biochemical effects of supplemented long-chain polyunsaturated fatty acids in hyperphenylalaninemia. Prostaglandins Leukot Essent Fatty Acids. 2001;64(2):111-5. https://doi.org/10.1054/plef.2000.0220

19. Demmelmair H, MacDonald A, Kotzaeridou U, et al. Determinants of Plasma Docosahexaenoic Acid Levels and Their Relationship to Neurological and Cognitive Functions in PKU Patients: A Double Blind Randomized Supplementation Study. Nutrients. 2018;10(12):1944. https://doi.org/10.3390/nu10121944

20. Teisen MN, Vuholm S, Niclasen J, et al. Effects of oily fish intake on cognitive and socioemotional function in healthy 8-9-year-old children: the FiSK Junior randomized trial. Am J Clin Nutr. 2020;112(1):74-83. https://doi.org/10.1093/ajcn/nqaa050