Fish oil supplementation improves visual evoked potentials in children with phenylketonuria
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cancer after liver transplant. Similarly, the rarity of clinically detectable metastases to liver or kidney in the general population and the occurrence of this complication in patients receiving transplants from glioblastoma patients lend credence to the concept that a systemically relatively intact immune system suppresses growth of extraneural glioblastoma metastases. The presence of an immune response against gliomas as reflected in lymphocytic infiltration of the tumor is associated with improved survival with the tumor.

Finally, we cannot exclude the possibility that this association between glioma and organ transplantation is coincidental. Our ongoing review of brain tumors in the Cincinnati Tumor Transplant Registry may further elucidate this issue.

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References

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Classic phenylketonuria (PKU) is one of the most prevalent inborn metabolic diseases, caused by deficient activity of hepatic phenylalanine hydroxylase.

Untreated patients experience severe psychomotor retardation. Early diagnosis and treatment with strictly limited protein intake and supplementation of phenylalanine-free synthetic amino acid mixtures result in largely normal cognitive development. However, minor psychomotor disturbances remain. The strict dietary treatment may induce metabolic imbalances and thus result in adverse effects. Among other micronutrients, docosahexaenoic acid (DHA) and other long-chain polyunsaturated fatty acids (LC-PUFA) are poorly supplied to PKU patients, because their natural food sources are rich in protein and hence avoided. Low blood concentrations of LC-PUFA have been described in PKU. LC-PUFA are essential components of cell membranes and modulate membrane functions. In healthy infants

**Article abstract**—Visual evoked potentials (VEP) were measured in 36 patients with early-treated phenylketonuria (PKU; aged 1 to 11 years) and good metabolic control before and after supplementation with omega-3 long-chain polyunsaturated fatty acids (LC-PUFA) from fish oil. Patients with PKU had significantly longer P100 latencies than 22 age-matched control subjects. After 3 months of LC-PUFA supplementation, VEP latencies improved significantly in PKU patients but did not change in 12 untreated healthy children. The authors conclude that omega-3 LC-PUFA are essential substrates for nervous system function even beyond infancy.

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fed with infant formula, LC-PUFA supplementation improves visual and psychomotor development.4,5 We hypothesized that children with PKU may benefit from supplementation with LC-PUFA and determined visual evoked potential (VEP) latencies as the outcome measure.

Subjects and methods. This open trial in classic PKU was approved by the Ethics Committee of the Bavarian Board of Physicians. All parents gave written informed consent before enrollment. Inclusion was restricted to otherwise healthy 1- to 11-year-old patients with an average plasma phenylalanine level, determined monthly over the previous 6 months, below 360 μmol/L.

At baseline, a clinical examination, routine blood tests (including phenylalanine concentration), and VEP were performed.

Patients were supplied with fish oil capsules (Ameu; Omega-Pharma, Berlin, Germany) at 15 mg of DHA/kg of body weight daily. Each capsule contained 500 mg of salmon oil (35% of omega-3 fatty acids: 18% of eicosapentaenoic, 12% DHA); the coating (gelatin) contained 3 mg of phenylalanine. Otherwise, dietary treatment remained unchanged. After 90 days, the clinical, laboratory, and VEP examinations were repeated.

Thirty healthy age-matched children (6.6 ± 0.5 years old, 15 girls) without dietary restrictions volunteered as control subjects. Written informed consent was obtained from the guardians.

Clinical examination and VEP were performed in all control subjects at baseline and repeated in a subgroup after 90 days. For ethical reasons, no blood sample was taken in control subjects, and they did not receive fish oil, as no substantial benefit from 3 months of supplementation could be expected in healthy children receiving a Western European mixed diet with an assumed regular DHA intake.

Thirty-eight patients with PKU from our outpatient clinic were included. Thirty-six completed the protocol (6.3 ± 0.6 years old, 19 girls). The diagnosis of PKU had been established by newborn screening and confirmed by further testing. Strict protein-restricted diets had been continuously followed from the first 3 weeks of life on.

VEP were performed with a Toennies NeuroScreen 1.63 (Jaeger-Toennies GmbH, Hoechberg, Germany; filter setting 1 to 100 Hz; sensitivity 20 μV/div; time base 30 ms/div). Subjects were exposed to a 3.2-Hz alternating black-and-white checkerboard pattern. Pattern size was modified for stimulation of the fovea (5’), the entire retina (30’) and two intermediate sizes (10 and 15’). All recordings were performed twice with 50 stimulations each. P100 latencies were determined independently by two experienced physicians. The investigators received all registrations in random order after completion of the protocol and were blinded with respect to subject group. Afterward, baseline and follow-up tracings of each individual subject were directly compared to ensure that corresponding peaks were chosen.

We applied Student’s t-test (comparisons between patients and control subjects) and t-test for paired samples (comparison of baseline and follow-up data), using SPSS for Windows (München, Germany). Significance was accepted at p < 0.05. Data are given as means ± SEM.

Results. Although most VEP were of very satisfactory quality, some recordings could not be evaluated with sufficient reliability. The proportions of paired VEP that were

| Table 1 | Latencies of visual evoked potentials in patients with phenylketonuria and healthy, age-matched control subjects at baseline (two sample t-test) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Checkerboard pattern | Patients, P100, ms | Controls, P100, ms | p, One-tailed |
| | Mean | SEM | n | Mean | SEM | n |
| 5’ | 133.0 | 1.4 | 30 | 124.1 | 1.3 | 24 | 0.00017 |
| 10’ | 119.6 | 1.2 | 22 | 116.5 | 1.3 | 19 | 0.046 |
| 15’ | 117.6 | 1.3 | 22 | 112.9 | 1.2 | 19 | 0.0059 |
| 30’ | 112.5 | 1.0 | 31 | 109.5 | 1.0 | 26 | 0.018 |

Table 2 Latencies of visual evoked potentials in patients with phenylketonuria and healthy, age-matched control subjects at baseline (two sample t-test)
Table 3 Visual evoked potential latencies in healthy children at baseline and after 3 months (follow-up) (t-test paired, two samples for means)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>5', n = 9</th>
<th>10', n = 12</th>
<th>15', n = 12</th>
<th>30', n = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>126.7</td>
<td>3.0</td>
<td>117.8</td>
<td>1.7</td>
</tr>
<tr>
<td>Follow-up</td>
<td>127.5</td>
<td>2.2</td>
<td>118.2</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Values are P100 latencies, expressed as milliseconds. No differences were significant.

accepted for further analysis were 61% for pattern size 10' and 15', 83% for 5', and 86% for 30'.

The mean latency of P100 was significantly prolonged in patients with PKU compared with control subjects in all stimulation modes (table 1). The largest difference was detected in foveal stimulation (pattern size 5').

Supplementation with fish oil led to a shortening of P100 latencies in PKU patients. Mean latencies tended to be shorter than at baseline in all stimulation modes, with significant differences for the foveal stimulation (5') and one of the intermediate pattern sizes (15'; table 2). There was no change in P100 latencies in the control subjects who could be re-examined (table 3).

The overall tolerance of the study drug was remarkably good (patients' judgment: "very good" 83%, "good" 11%, "moderate" 6%). Six minor adverse events (fifteen viral gastroenteritis, one slight epistaxis) were observed. A causal relationship to fish oil administration was considered doubtful in all cases. Dosing adjustment or interruption was not necessary. Vital parameters (heart rate, blood pressure) and routine laboratory parameters (liver enzymes, platelet count, and coagulation tests) revealed no relevant alterations. Plasma phenylalanine concentrations did not change during the intervention period (see table 2).

Discussion. The strictly treated PKU patients investigated in this study showed delayed VEP latencies compared with healthy control subjects. The remarkably similar variance of test results indicates that this phenomenon characterizes treated PKU in general, rather than reflecting single pathologic recordings. The recently reported LC-PUFA deficiency in PKU might be responsible. DHA has important functions in the assembly, maintenance, and function of cell membranes and is a major PUFA in structural brain phospholipids. It is also highly concentrated in synaptosomal membranes. Endogenous synthesis of DHA from α-linolenic acid found in vegetable oil is rather inefficient in humans. Several studies in newborns and infants have recognized the role of DHA in the postnatal development of the visual system and cognition.

The importance of DHA supply is supported by the significant improvement of VEP latencies upon administration of fish oil that provides large amounts of DHA. The change of VEP latencies is not a normal developmental process, as the control group had unchanged VEP latencies after the same follow-up period. Large studies in healthy children showed that P100 latencies shorten rapidly during the first year of life but remain stable thereafter.

During the preparation of this manuscript, similar results were reported. Supplementation of 10 PKU patients with fish oil (10 mg of DHA/kg of body weight daily) for 12 months resulted in a normalization of formerly delayed 15' pattern reversal VEP and 2-Hz flash VEP. In the placebo-treated patients, these recordings were unchanged, whereas 1-Hz flash VEP were also normalized. Thus, long-term supply of DHA may be necessary to completely normalize the delay of signal transduction.

A placebo-controlled blinded randomized trial would have been desirable, but only an open trial enabled us to apply strict inclusion criteria and still recruit a sizeable patient number. The electrophysiologic nature of the outcome measure and stable results in the healthy control subjects make us confident of demonstrating a real effect of the intervention. In view of functional benefit and absence of adverse effects, addition of LC-PUFA to the PKU diet should be considered. Further evaluation in larger groups of PKU patients is necessary, testing potential effects on other functional outcomes, monitoring fatty acid plasma concentrations, and approaching optimal dosage.

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References

Benign nocturnal alternating hemiplegia of childhood: Six patients and long-term follow-up

In a series of eight children with alternating hemiplegia, two siblings with exclusively nocturnal onset of hemiplegic episodes and favorable outcome were described. We then reported two brothers with recurrent attacks of alternating or bilateral hemiplegia that also arose exclusively out of sleep and stressed that these children had neither dystonic attacks, paroxysmal eye movement abnormalities, nor permanent hypotonia or other features characteristic of the classical sporadic form of alternating hemiplegia of childhood (AHC) and that their mental and motor development remained normal. We distinguished “benign familial nocturnal alternating hemiplegia of childhood” (BNAHC) from the classic malignant form of alternating hemiplegia of childhood.

We here report two additional patients with episodes of alternating hemiplegia developing during sleep and present a review of clinical data, investigations, and long-term follow-up of all patients described to date.

Case reports. Patient 1. A 5.5-year-old Zairian boy developed episodic hemiplegic attacks at 22 months of age. He awoke from sleep screaming, and his mother found him with one side limp and paralyzed and his mouth distorted. A family video showed that the face and arm were flaccid while the leg was paretic, allowing him to stand. He was drooling, seemed conscious, but did not answer questions and had a Babinski sign on the affected side. Episodes were never bilateral. Initially, frequency was two to four times per month and was not modified by treatment with either flunarizine or carbamazepine. The patient has had no treatment for almost 2 years, and now has one to two episodes per month. He has no recollection of the attacks and is unable to describe them. Recently, his mother has observed prodromal symptoms of headache, irritability, and oppositional behavior, occurring during the 3 days preceding an episode.

Patient 1 was born after normal pregnancy and delivery and had normal Apgar scores. Birth weight was 3.3 kg. He walked at 9 months. Psychomotor development is normal, and he does well in a normal pre-elementary school but is mildly hyperactive. He had iron deficiency anemia, but treatment did not alter the frequency of the attacks. He was diagnosed to be a heterozygote for β-thalassemia. At 3.3 years of age, he had a thyroglossal cyst removed. Thyroid function was normal.

He has healthy twin brothers and a sister. His mother experiences migraine with visual aura, and a maternal great aunt had uncharacterized hemiplegic attacks during wakefulness. She drowned during such an attack in early adulthood. Family history on the father’s side is unknown.

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