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Omega-3 Long-Chain Polyunsaturated Fatty Acids in Older Children

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Phenylketonuria (PKU), the most prevalent inborn error of metabolism, is usually secondary to low hepatic activity of phenylalanine hydroxylase, the enzyme that catalyzes conversion of phenylalanine to tyrosine (1). It is characterized by a high plasma phenylalanine concentration and, in the absence of adequate tyrosine intake, a low plasma tyrosine concentration. Management of patients with PKU includes early detection, primarily by mandatory neonatal screening programs, followed by a low protein diet supplemented with a low-phenylalanine or phenylalanine-free formula. Frequent monitoring and appropriate dietary changes in response to this monitoring are necessary to maintain plasma phenylalanine and tyrosine concentrations within the desired range.

Growth and development of infants and children with PKU who are managed as described above do not differ appreciably from population norms. However, the IQ of well managed children with PKU is somewhat lower than that of their unaffected siblings (2). These children also perform less well in school than their unaffected siblings, they tend to exhibit more behavioral problems and they have problems concentrating. Nonetheless, current outcomes of infants and children with PKU are far superior to the severe psychomotor retardation that occurs without treatment.

A major question concerns the extent to which the residual developmental deficits of optimally managed infants and children with PKU are an inevitable consequence of the condition. A study reported by Beblo et al. (3) in this issue of *The Journal of Pediatrics* suggests that at least some of the residual deficits can be further reduced or perhaps abolished by dietary supplementation with fish oil, a rich source of ω -3 long-chain polyunsaturated fatty acids (LC-PUFA), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The latter fatty acid has received considerable attention over the past 20 years. It is present in high concentrations in the developing brain and retina and failure to provide a dietary source of this fatty acid results in low plasma, erythrocyte and brain lipid levels of DHA (4). Many studies also show that failure to provide a dietary source of DHA adversely affects cognitive and visual development (4). Thus, most infant formulas throughout the world now contain DHA or this fatty acid plus arachidonic acid (AA). The amounts present reflect the content of these fatty

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acids in human milk. Although the majority of studies have involved short periods of supplementation during early life, usually for only a few months and almost never beyond the first year of life, these supplemented formulas appear to be safe.

Despite the fact that the rate of deposition of DHA in the developing brain does not slow appreciably until well after a year of age (5), little is known about the need for a dietary source of this fatty acid by children older than 12-to-18-months. This is unfortunate because the endogenous production of DHA from its precursor, α -linolenic acid, is thought to be inefficient and intake of preformed DHA (e.g., fish) by most children (and many adults) is quite low.

Beblo et al. studied 1-to-11-year-old (mean = 6.3 ± 0.6 y) children with PKU who had been in good metabolic control for at least 6 months as well as a control group of unaffected age- and gender-matched children. After determining plasma phospholipid fatty acid pattern and administering the motometric Rostock Oseretzki Scale, a standardized scale which assesses coordination and fine motor skills of children between 4 and 11 years of age, the patients received fish oil (~15 mg/kg/d of DHA and ~22.5 mg/kg/d of EPA) for 90 days after which the baseline studies were repeated. Baseline plasma phospholipid DHA content of both the children with PKU and the controls was low but not different from that of a reference population from the same geographic region. Fish oil supplementation of the children with PKU resulted in a 3-fold increase in plasma phospholipid DHA content, an 8-fold increase in plasma phospholipid EPA content and a 25% decrease in plasma phospholipid AA content. Baseline performance assessed with the standardized test of coordination and fine motor skills was within the normal range in both patients and controls but performance of the control children was better than that of the children with PKU. However, after fish oil supplementation, performance of children with PKU was markedly improved whereas the performance of controls (who did not receive fish oil or have plasma phospholipid fatty acids repeated) was not different from baseline.

These investigators (6) as well as other groups (7) have previously shown that ω -3 LC-PUFA supplementation of patients with PKU lowers visual evoked potential (VEP) latency and that the magnitude of decrease in latency is associated with the observed increase in DHA content of erythrocyte lipids. Still other studies have shown that the difference in VEP latency is not apparent 3 years after terminating supplementation (8) suggesting that a continuous supply of ω -3 LC-PUFA may be required. In contrast, children with PKU who were breastfed (and, hence, received DHA) for up to 6 weeks prior to beginning dietary therapy had a 12.9 point higher IQ at 9 years of age (after adjustment for social class and maternal education) than infants who were formula-fed for the same period (9). Metabolic control of the two groups after diagnosis and beginning dietary therapy did not differ.

In toto, the study of Beblo et al. (3) adds considerably to an existing body of data suggesting that ω -3 LC-PUFA may be conditionally essential for infants and children with PKU. This, presumably, is because the usual PKU diet is low in protein and, hence, low in the common dietary sources of ω -3 LC-PUFA (e.g., fish; meat; eggs). This also appears to be true for other nutrients, for example, formulas for patients with PKU are supplemented with several essential trace minerals and vitamins that have been shown to be low in low protein diets or poorly available from these diets.

The improvement of older children with PKU secondary to ω -3 LC-PUFA supplementation, without changes in plasma phenylalanine concentration, suggests that still other groups might benefit from dietary ω -3 LC-PUFA. Certainly, the brain continues to grow until well beyond infancy (5) and there likely is considerable turnover of brain components, including DHA, after adult size is reached; thus, there may be benefits of ω -3 LC-PUFA supplementation, not only during infancy and early childhood but also, perhaps, during adolescence and adulthood.

Currently, evidence that children with PKU might benefit from ω -3 LC-PUFA supplementation, perhaps as a component of their low phenylalanine formula, is reasonably strong. However, whether this supplement should be EPA, DHA or perhaps both, as studied by Beblo et al. (3), is not clear. The amount of these fatty acids that should be provided also is not clear. An 8% increase in plasma phospholipid EPA content, as reported by Beblo, et al. (3) seems somewhat excessive. Further, considering the 27% decrease in plasma phospholipid AA observed by Beblo et al. (3), the supplement perhaps should also include ω -6 LC-PUFA.

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