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**Commentary**

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# Long-Chain ω-3 Polyunsaturated Fatty Acids: Do Genetic Steps Match Metabolic Needs?

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The >30-y connection between long-chain PUFAs (LC-PUFAs), brain development and disease modulation, particularly in the pediatric age, has been characterized by exciting hypotheses and preliminary observations, followed by contrasting (often frustrating) observations, and, even more, inconclusive systematic reviews and meta-analyses (1).

LC-PUFAs are synthesized by elongation of the fatty acid carbon chain and insertion of double bonds (i.e., desaturation) from the parent essential linoleic acid (LA) for the ω-6 series and α-linolenic acid for the ω-3 series (2). The most important byproducts are the ω-6 arachidonic acid (AA) and the ω-3 DHA, whose balance has been associated with major functional developmental outcomes and inflammatory reactions. The major rate-limiting enzymes are represented by Δ5- and Δ6-desaturases, which are encoded by the genes *FADS1* and *FADS2*, respectively (3, 4). Accordingly, polymorphisms in fatty acid desaturase genes might modulate the functional effects of LC-PUFAs, and could help to identify those subjects taking advantage from an exogenous dietary supply due to poorer endogenous synthesis rates. Yet, contrasting data have been published, starting from the different effects of LC-PUFA supply through the first dietary source, that is human milk, in infancy and functional outcomes such as intelligence quotient scores (5, 6) or the risk for allergy-related disorders such as asthma (7). The analysis of genetic variability at the elongase steps has been considered too, adding more precision but also difficulties in the interpretation of functional associations, where gender may play a further role (8). In the present issue of the Journal, a study in mice by Yakah et al. (9) sheds light on a further step in the utilization of circulating LC-PUFAs at the level of transporters and their expression. In their experimental design, the authors studied the brain and lung transporter expression in 2 murine models, C57BL/6 wild-type and *Fat1* mice, respectively. The first model reflects a fatty acid status with predominant compounds of the ω-6 series following a Western-like diet (wild-type), whereas the second maximizes a fatty acid pattern enriched in ω-3 LC-PUFAs since transgenic *Fat1* mice express the *Caenorhabditis elegans Fat1* gene encoding an ω-3 fatty acid desaturase able to convert ω-6 PUFAs to ω-3 PUFAs.

The researchers hypothesized that fatty acid transporter expression is developmentally regulated and tissue specific, with the possibility to modulate the accretion of DHA and AA independently of diet in newborns. They observed (at developmental ages corresponding to preterms, 2–8 mo, and 4–8 y of age in humans, respectively) that the transporter expression is tissue specific but, in contrast to the original hypothesis, the fatty acid profiles, particularly brain DHA and its precursor, EPA but not AA, is altered by diet alone independent of the transporter status. According to these experimental data, diet could represent a major driver of ω-3 LC-PUFA availability at brain level throughout the whole developmental age, independent of transporter status and possible regulatory feedback mechanisms.

These findings are consistent with data published in humans, showing that DHA synthesis (but not AA) decreases after 7 mo of life in infants born preterm (10), corresponding to one of the experimental ranges of age studied by Yakah and coworkers (9), thus suggesting a higher dependence on dietary sources for DHA at this stage. Beyond the pediatric age, within a large population of more than 700 white adults no association was found between genetic variants and DHA variance, supporting the hypothesis that little DHA is synthesized endogenously, and serum DHA concentrations are primarily determined by the dietary supply of preformed DHA. On the contrary, genetic variants explained as much as 28.5% of the variation in serum AA (11). If these observations could be further confirmed throughout the life span, the clinical meaning would be even more striking, suggesting the possibility of preserving neurocognitive functions, and even treating psychiatric disorders (12, 13).

On the whole, data in humans, from plasma total lipids to whole blood fatty acids, from membrane fatty acid composition to human milk, show a relative stability of AA levels, compared to DHA (and EPA too). Therefore, a genetic control of the levels of AA, crucial to the synthesis of eicosanoids, essential for adaptation to different life conditions and then survival, is a reasonable hypothesis. On the other hand, ω-3 LC-PUFAs, and primarily DHA, are clearly subject to environmental variables, especially dietary intake. Among dietary LC-PUFAs, DHA is preferentially channeled into the brain phospholipids of human infants, as Farquharson (14) has shown in autopsy studies of the forebrain of cot-death infants. Indeed, among the 2 major LC-PUFAs, DHA predominated in the case of those babies fed human milk, the first natural source of preformed DHA and AA, while AA predominated in those fed infant formulas that did not contain any preformed LC-PUFAs, suggesting a superior genetic control for AA stability in the brain matter following a facilitated synthesis rate from LA.

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We hypothesize that during human evolution, AA has been selected for the preservation of life through adaptive mechanisms, primarily the inflammatory response, whereas DHA has developed a qualitative role within specialized membranes, thus influencing brain function above all (15, 16). But the advantages of a given balance between the 2 compounds, DHA and AA, may not be unequivocal, either in health status for preventive purposes or in counteracting inflammatory conditions in chronic reactive disorders. The clearest example may be represented by cystic fibrosis, where AA levels are maintained at the expense of LA, suggesting an increased turnover of the $\omega$-6 series to replenish the eicosanoid pool, while DHA could be consumed to counteract unfavorable inflammatory reactions (17). Even in this case, convincing evidence of a favorable functional effect of DHA dosages used to down-modulate the generalized inflammatory reactions in cystic fibrosis is still lacking (18). Much speculation is possible, including the possibility that AA could have some still unexplored regulatory effects that counteract the anti-inflammatory properties of DHA. Alternatively, much higher DHA doses could be necessary to overcome the proinflammatory effects of eicosanoid compounds derived from AA. Paradoxically, both explanations could be plausible, in spite of being apparently contrasting (like several situations in biomedicine). Even considering the observations reported herein by Yakah et al., we are not able to fully explain the meaning of decreasing transporter activity with age in brain cells accompanied by higher DHA levels. Yakah et al. finally suggest that "deficiencies in systemic fatty acid status should raise the concern of inadequate dietary delivery". Accordingly, well-conducted dietary enrichment with $\omega$-3 LC-PUFAs could relieve the inadequate individual status. More importantly, it is also suggested that "if insufficient fatty acid status persists despite nutritional intervention, other non-transporter related issues should be considered such as the developmental and genetic capability of adequate digestion, absorption, and downstream conversion". Further studies should address the issues on digestion and absorption of fatty acids (particularly preformed $\omega$-3 LC-PUFAs), whose relevance in determining the individual fatty acid status (including the availability from different biochemical carriers and combinations with other nutrients) has been poorly explored so far despite early suggestive reports (19). More detailed knowledge of these steps could give further indications to overcome the contrasting data now arising from studies that we formerly expected to provide more resolution (such as those on the genetic variability of the LC-PUFA biosynthetic pathway).


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