Prenatal and early postnatal long-chain polyunsaturated fatty acid status
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Summary

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5 Summary

5.1 Introduction
Long-chain metabolites of the parent essential fatty acids called long-chain polyunsaturated fatty acids (LCPUFAs) are major membrane components in the central nervous system. Dietary intake partly determines the availability of LCPUFAs as building blocks for neuronal structures. Fifty till sixty percent of the dry brain weight consists of fatty acids of which about twenty percent are LCPUFAs. In particular two LCPUFAs, docosahexaenoic acid (DHA) and arachidonic acid (AA) are being incorporated into neuronal tissue. Conversion of the essential fatty acid alpha-linolenic acid into DHA is inefficient in humans, so DHA status is relatively dependent on dietary intake of DHA, which is currently low in western societies. Many studies have provided evidence that DHA and AA play a role in adequate functioning of the central nervous system. During the so-called brain growth spurt, which takes place shortly before and after birth until about the age of 2 years, large amounts of fatty acids are being incorporated into the nervous system. It is therefore remarkable that conventional formula feeding does not contain LCPUFAs, whereas breastfeeding does contain LCPUFAs. LCPUFAs could partially explain the observed positive effect of breastfeeding on neurodevelopment.

To study the potential beneficial effects of LCPUFAs and the type of early postnatal feeding on neurodevelopmental outcome we investigated 472 healthy term infants in a double blind randomized controlled trial with a breastfed reference group. Follow-up after two months of LCPUFA supplementation was conducted at the ages of 3 and 18 months to evaluate neurodevelopmental outcome. In addition, we evaluated the relationships between prenatal LCPUFA status and the neurodevelopmental outcome at 3 and 18 months in the same study cohort. For this we collected samples of the umbilical vein and artery for the determination of the LCPUFA content. The LCPUFA content was used as a marker of prenatal LCPUFA status (See also Chapter 1, figure 5).

5.2 Is postnatal LCPUFA supplementation beneficial for neurodevelopment?
The addition of LCPUFAs to standard formula for the duration of two months did improve the quality of general movements (GMs) at the age of 3 months (Chapter 2 §2.1). The evaluation of the GMs has proven to be a sensitive technique for evaluating the quality of brain function in young infants. The quality of GMs was classified into normal optimal, normal suboptimal, mildly abnormal and definitely abnormal. No definitely abnormal GMs were observed, which is in agreement with data from a healthy term study population. A significant reduction in the presence of mildly abnormal general movements was observed in the LCPUFA supplemented formula group compared with the control formula group. When expressed as ‘numbers needed to treat’, eight infants have to supplemented with LCPUFA to prevent the occurrence of one infant with mildly abnormal GMs. Breastfed infants showed more optimal GMs compared with the formula-fed groups after correction for confounders. To investigate the minimal duration of exclusive breastfeeding for optimal neurological condition at 3 months, a subgroup analysis in the breastfeeding group was performed. The median duration of breastfeeding was 9 weeks. Inspection of the association between the duration of exclusive breastfeeding and the quality of GMs revealed that there was a positive association between the duration of exclusive
breastfeeding and the quality of GMs. Close inspection of the raw data revealed that a saturation effect occurred at the age of ≈6 weeks. Infants who had received breastfeeding for more than 6 weeks had more optimal GMs and less mildly abnormal GMs at 3 months (Chapter 2 §2.2). Our study could not answer the question whether breastfeeding for longer periods would be even better for the neurological condition, as only few mothers breastfed their infant for more than 12 weeks and because we assessed outcome as early as 3 months. The beneficial effect of LCPUFA supplementation at the age of 3 months was no longer observed at the age of 18 months as measured by the Bayley Scales and the neurological examination according to Hempel. Breastfeeding also did not enhance neurodevelopmental outcome at 18 months.

To summarize, it seems that the beneficial effects of LCPUFA supplementation are present at 3 months and disappear prior to the age of 18 months at which age it is notoriously difficult to find differences in motor and cognitive performance. The absence of difference between the feeding groups however does not preclude the finding of differences at later ages when complex neurological circuitries have become functionally active. Therefore, a follow up at school age is currently performed to evaluate the long-term effects of LCPUFA supplementation in the same study population.

5.3 Prenatal fatty acid status and neurodevelopmental outcome

In addition to the evaluation of the influences of postnatal feeding on neurodevelopmental outcome, we assessed the influences of prenatal nutrition by measuring the fatty acid composition of the umbilical vessels shortly after birth. Chapter 3 describes the associations between the fatty acid composition of the umbilical vessels, a proxy of prenatal fatty acid status, and the neurodevelopmental outcomes at 3 and 18 months. Infants showing mildly abnormal GMs had a lower AA, DHA and essential fatty acid status in the umbilical artery (Chapter 3 §3.1). Therefore, infants with mildly abnormal GMs could have a less favourable LCPUFA profile at birth than infants with normal GMs.

No correlations were found between the prenatal fatty acid status and the Bayley score at 18 months. However, the more sensitive neurological examination according to Hempel revealed that the fatty acid composition of the umbilical vein correlated with the neurological optimality score at 18 months. Infants with an umbilical vein DHA status within the lowest quartile had a lower neurological optimality score compared to infants with a higher umbilical DHA status. The mean effect size was about 1-2 points on a scale with a maximum of 57 points. The significant association between arachidonic acid status and the neurological optimality score disappeared when correcting for confounding factors. The latter finding confirms that the observed relationships between prenatal LCPUFA supply and neurodevelopmental outcome are subtle at best.

Apart from the relationship between prenatal LCPUFA status and neurodevelopment, we were also interested in the potential harmful effects of trans fatty acids on neurological development because of the reported inhibitory effect of trans fatty acids on LCPUFA synthesis in the literature. Surprisingly, we found that prenatal trans fatty acids exhibited an even stronger negative relationship with the neurological condition at 18 months than prenatal LCPUFA status. The mean difference in the neurological optimality score between the lowest and the highest quartile of trans fatty acid content was about 3 points. This means that infants who are exposed to relatively high levels of trans fatty acids in utero was associated with a somewhat less quality of motor behaviour which for instance can
become manifested by a lesser ability to avoid objects, less fluent movements and less variations in motor behaviour. Remarkably, our results indicated that prenatal nutritional influences on neurodevelopment were stronger than influences of type of postnatal feeding, i.e. either breastfeeding or infant formula feeding.

5.4 Conclusions
The development of the infant is a complex interplay between genetics and environment in which LCPUFA status plays a role. The following conclusions can be drawn from the studies described in this thesis:

- LCPUFA supplementation (0.30% DHA and 0.45% AA) in formula feeding for two months significantly reduces the occurrence of mildly abnormal general movements at the age of 3 months in a population of healthy term infants;
- Infants who received breastfeeding for more than 6 weeks had less mildly abnormal general movements at 3 months compared with infants who received breastfeeding for 6 weeks with or without correcting for confounding factors;
- Infants who received breastfeeding or LCPUFA supplemented formula feeding had a similar neurodevelopmental outcome at 18 months as measured with the Hempel assessment and the Bayley Scales compared with the standard formula fed infants;
- Prenatal LCPUFA status and trans fatty acid content was related with neurodevelopmental outcome at 3 and 18 months even when type of postnatal feeding was taken into account;
- Infants who had mildly abnormal general movements at 3 months had a less favourable prenatal LCPUFA status;
- Prenatal DHA status within the lowest quartile was associated with a less favourable quality of motor behaviour at 18 months;
- Prenatal trans fatty acid content was negatively associated with the quality of motor behaviour at 18 months.
- Prenatal fatty acid status might be more important as a determinant for neurological condition than type of postnatal feeding (breastfeeding, LCPUFA or standard formula feeding).