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Neonatal fatty acid status and neurodevelopmental outcome at 9 years

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ABSTRACT

Background: Long-chain polyunsaturated fatty acids (LCPUFA) are important for prenatal brain development. Previous studies of others assessed outcome until 7 years. The associations between neonatal LCPUFA status and long-term developmental outcome are debated.
Aim: To investigate the relationship between fatty acid status at birth and neurodevelopment at 9 years. Age 9 is a unique age after a significant neurodevelopmental transition.
Study design: Correlation study. Multivariable analyses were carried out to adjust for potential confounders.
Subjects: 317 children who participated in a trial on effects of postnatal LCPUFA supplementation were eligible. 235 children (74%) were reassessed at age 9.
Outcome measures: At birth, docosahexaenoic acid (DHA) and arachidonic acid (AA) were determined in the wall of the umbilical vein. We primarily studied the correlation between DHA and AA with the complex form of minor neurological dysfunction (cMND). Secondary correlations that were studied were DHA and AA levels with cognitive development in terms of full IQ, and with behavioural development in terms of a total problem score.
Results: Boys with cMND showed lower DHA values in the umbilical vein than children with better neurological condition ($p = 0.033$). A similar association was absent in girls. Neonatal AA values were not associated with neurological outcome. Neither neonatal DHA nor AA values were associated with cognition and behaviour at 9.
Conclusions: Higher umbilical DHA levels in boys are associated with better neurological development at 9 years. AA status at birth was not associated with neurodevelopment at 9 years.

1. Introduction

The human nervous system increases rapidly in size and complexity during pregnancy. Adequate supply of necessary nutrients such as long-chain polyunsaturated fatty acids (LCPUFA) to the foetus is essential for optimal neurodevelopment.

Studies on the effects of docosahexaenoic acid (DHA) or fish oil supplementation during pregnancy on neurodevelopmental outcome provided inconsistent results [1,2]. Observational studies on the relationship of neonatal DHA, arachidonic acid (AA), and essential fatty acid status with neurological outcome from preschool age to 7 years reported associations with early DHA status only [3,4]. Most studies using cognitive development as outcome measure demonstrated no associations with early LCPUFA status [3,5], except for the study of Boucher et al. [6]. The latter study reported a significant positive association between neonatal DHA and memory at school age. Data on the relation between behavioural development and LCPUFA are scarce. The only study that we are aware of reported no associations between neonatal LCPUFA status and behaviour at preschool age [7].

The current study is part of the Groningen LCPUFA study, a randomised controlled trial on the effect of postnatal supplementation of LCPUFA on the neurodevelopment of healthy term infants. The study revealed that postnatal LCPUFA supplementation was not associated with a consistent effect on neurodevelopmental outcome at 9 years [8,9]. In a subgroup, the fatty acid status in the umbilical cord was analysed in order to study the contribution of intrauterine LCPUFAs to child development. The aim of the present paper is to evaluate in this subgroup the relationship between the relative DHA and AA levels in the wall of the umbilical vein and neurological, cognitive, and behavioural outcome at 9 years. The age of 9 years is the time after a significant neurodevelopmental transformation, which occurs between 7 and 9 years of age [10]. This is the age at which many minor

Abbreviations: LCPUFA, Long-chain polyunsaturated fatty acids; DHA, Docosahexaenoic acid; AA, Arachidonic acid; MND, Minor neurological dysfunction; IQ, Intelligence quotient; OOS, Obstetrical optimality score; BMI, Body mass index; CBCL, Child behavioural checklist; TRF, Teacher report form.

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dysfunctions of the nervous system emerge [11]. Primary outcome is neurological condition in terms of minor neurological dysfunction (MND). We focus on complex MND, which is the clinically relevant form of MND. Secondary outcome variables are cognition, i.e., intelligence quotient (IQ), and behaviour. Specific attention was paid to possible interactions between neonatal fatty acid status and A) sex, as a previous study suggested that in particular girls may benefit from early DHA supply [12], and B) smoking during pregnancy, which is known to interact with postnatal LCPUFA supplementation [9].

2. Method

2.1. Study population and design

The study was part of a double-blind randomised controlled trial investigating the effect of LCPUFA supplementation on development in healthy, term infants and was powered on developmental outcome at 18 months (the Groningen LCPUFA study; for details, see Bouwstra et al. [13]. Pregnant women were recruited between 1997 and 1999; mothers of 314 infants chose to bottle feed and 160 opted for breastfeeding. The infants receiving formula were randomised into a standard formula group (control formula, n = 169) and a LCPUFA-supplemented formula group (n = 145). The standard formula was Nutrilon Premium (Milupa, Friedrichsdorf, Germany). For the supplemented formula, the lipid fraction of Nutrilon Premium® was enriched with 0.45% (by wt) AA and 0.30% (by wt) DHA. The duration of supplementation was 2 months. In case breastfeeding stopped prior to 2 months (n = 49), the infant received LCPUFA-supplemented formula till the age of 2 months. All formula-fed infants received control formula between 2 and 6 months.

Parents of 317 infants gave permission to obtain umbilical cord tissue (67% of the original population, see Fig. 1). Seven- to ten-centimetre samples of umbilical cord were collected shortly after parturition. Details on collection and processing of the cords can be found in Bouwstra et al. (2006) [3]. Neurological condition was assessed at 3 and 18 months. All 290 children assessed at 18 months (91.5% of the original groups) were eligible for re-examination at 9 years. At the 9-year follow-up, both parents and examiners were unaware of the type of formula-feeding the infant had received and of neonatal fatty acid status. The examiners were also blind to formula versus breast status. The study was approved by the Ethics Committee of the Groningen University Hospital. The trial is registered under ISRCTN52788665. Depending on the wish of the participants, the neurological and cognitive assessment at the age of 9 years was carried out in the hospital or at home.

2.2. Analysis of the fatty acids of the umbilical vessels

Data were expressed as percentages of weight of fatty acids with a chain length of 14–24 carbon atoms. DHA and AA status were based on their respective levels [3].

2.3. Neurological assessment

Neurological condition of the children was evaluated with a standardised, age-specific assessment designed for the assessment of MND [14]. Essential in the diagnostics of MND is that single signs do not have clinical significance; signs only have significance when they co-occur with other signs within a functional domain. The examination is organised into eight functional domains: posture and muscle tone, reflexes, dyskinesia, coordination, fine manipulative ability, associated movements, sensory deficits, and cranial nerve functioning. The examination results in a clinical classification in four categories: normal, simple MND, complex MND, and abnormal. A child is considered neurologically abnormal in case of the presence of a clear neurological disorder, such as cerebral palsy. Simple MND denotes the presence of one or two domains of dysfunction and is present in about 15–20% of children. It has little clinical relevance and can be regarded as a sign of typical but non-optimal brain functioning. Complex MND denotes the presence of more than two domains of dysfunction and is the clinically relevant form of MND. In an aetiological sense, complex MND can be considered as a borderline form of cerebral palsy as it is linked to pre- and perinatal adverse events [15]. A child is classified as neurologically normal if no domains are scored as deviant or in case of the isolated presence of a mild dysfunction in reflex activity.

The MND assessment has a good intrarater, interrater, and test–retest reliability; the kappa statistics of the three forms of reliability for neurological classification ranges between 0.71 and 0.83 [14]. Its construct

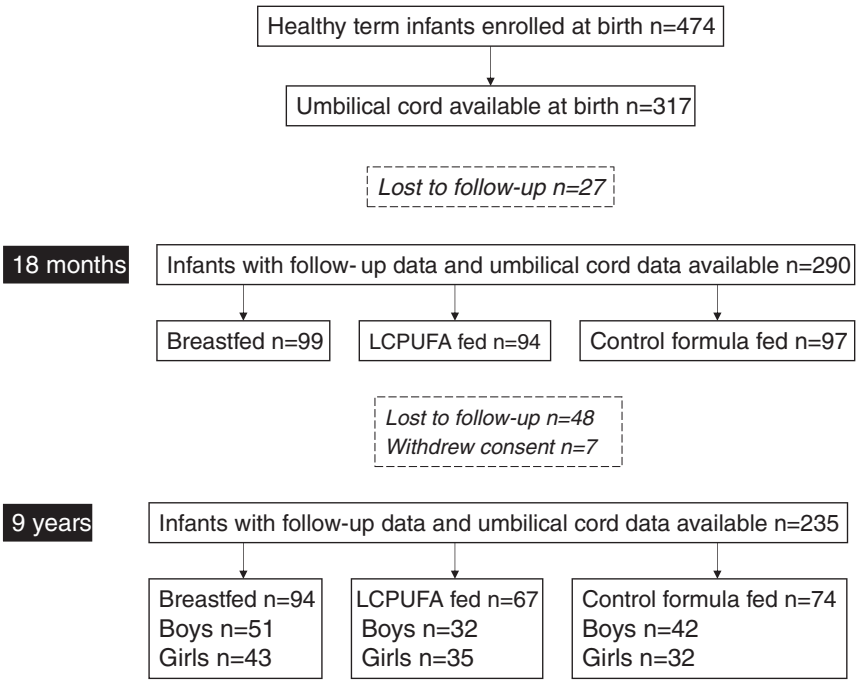

Fig. 1. Flow diagram of children enrolled in the study and followed up until 9 years of age. *For more detailed information see Bouwstra et al., 2006 [3].