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EARNest

EARly Nutrition programming- long term follow up of Efficacy and Safety Trials and integrated epidemiological, genetic, animal, consumer and economic research

Instrument: Integrated Project

Thematic Priority 5.4.3.1: Food Quality and Safety

Final public report on activity 1.3.1

Evaluation of long term effects of prenatal and early postnatal LCPUFA status on neurodevelopmental outcomes and on growth and blood pressure

Period covered from 15.04.2005 to 14.10.2010

Start date of project: 15.04.2005

Duration: 5,5 Years

Organisation Name of Lead Contractor for this report: UMCG

THE GRONINGEN LCPUFA-COHORT

Introduction

The central nervous system contains a high level of long-chain polyunsaturated fatty acids (LCPUFA). LCPUFA accrue rapidly in the grey matter of the brain during development, in particular during the last trimester of gestation and the first weeks after term age. LCPUFA status during early infancy and LCPUFA supplementation of formula feeding has a beneficial effect on visual and neuromotor development in early infancy. But it is debated whether LCPUFA can affect neurodevelopmental outcome of term infants beyond the age of one year. Possibly, LCPUFA do not affect global measures of long term neurodevelopmental outcome, but only specific ones, such as neural functions which heavily rely on cortical-subcortical circuitries.

This EARNEST activity aimed at evaluating the effect of a) LCPUFA supplementation of formula feeding during the first two postnatal months and b) neonatal fatty acid status (based on fatty acid composition of umbilical vessels) on specific parameters of neurodevelopmental outcome, which are dependent on the integrity of (sub)cortical pathways at the age of nine years in the Groningen LCPUFA cohort. Prior to EARNEST the 457 healthy term infants of the cohort participated in a prospective double-blind randomized control study on the effect of LCPUFA supplementation for the duration of two months on neurodevelopmental outcome till 18 months of age (attrition 8%). At birth the children were allocated into three groups, a control formula (CF) group (n=162), a LCPUFA-supplemented formula (LF) group (n=139) and a breast-fed (BF) group (n=156). Standard formula consisted of Nutrilon Premium®. For the supplemented formula, the lipid fraction of Nutrilon Premium® was enriched with 0.45% (by wt) Arachidonic Acid (AA, member of the omega-6 fatty acids) and 0.30% (by wt) Docosahexaenoic Acid (DHA, member of the omega-3 fatty acids). The BF group served as a reference group. In 310 children fatty acid status could be determined in umbilical vessels.

Subjects and methods

All children of the LCPUFA cohort who were tested at 18 months were invited for follow-up at 9 years (n = 436); 341 of the 474 children of the original study agreed to participate, 91 children in the LF-group (63%), 123 children in the CF-group (73%) and 127 children in the BF-group (79%). This means that overall attrition was 28%, which is relatively good for a 9-year follow-up in a non-clinical population. However, for unexplained reasons, attrition was selective: drop-outs in the LF group were more often boys and had a significantly lower mental developmental index at 18 months.

Children with tested with an extensive neurodevelopmental assessment battery. It consisted of

- a standardized age-specific neurological examination according to Touwen (1979). This assessment allows for a detailed assessment of neurological condition. Outcome is expressed in terms of minor neurological dysfunction (MND; severity and type) and in a neurological optimality score (NOS)
- Intelligence was assessed using the WASI – Wechsler Abbreviated Scale of Intelligence¹³. This test results in a Full IQ (FIQ) score which can be divided into a Verbal IQ (VIQ) score and a Performance IQ (PIQ) score.
- Specific cognitive performance was assessed by means of the NEPSY, the Tea-ch and the Children's Memory Scale. The NEPSY provided information on 1) Attention and Executive Functions, 2) Memory and Learning ability, and 3) Language ability (Comprehension of instructions and Speeded naming). The Tea-ch – Test of Everyday

Attention for Children furnished information in three domains of attention: 1) Selective attention, 2) Sustained attention, and 3) Attentional control/switching. In addition verbal memory was assessed to delineate the verbal aspects of memory, to this end the Word Pair subtask of the Children's Memory Scale was used.

- Behaviour was evaluated by means of parental and teacher's questionnaires, i.e. the Dutch versions of the Children's Behavioural Check List (CBCL), the Teacher Report Form (TRF) and an additional questionnaire on ADHD.

In addition, anthropometrics (height, weight, body mass index, head circumference) were measured and heart rate, systolic and diastolic blood pressure was recorded with a Datascope Accutorr plus.

Data-analysis first focused on the effect of postnatal nutrition, in particular on the effect of LCPUFA supplementation. Next the data on neonatal fatty acid status were correlated with outcome parameters. In all analyses multivariate statistics were performed to adjust for confounding factors. Many factors were taken into account, varying from details on prenatal and perinatal condition, social economic status, current diet and maternal IQ.

Findings

Effect of postnatal nutrition:

1. *Neurological condition:* Neurological optimality and severity and type of minor neurological dysfunction (MND) at 9 years did not differ between the LF and CF groups. Children in the BF group showed significantly less often fine manipulative dysfunction than formula-fed children. We therefore concluded that LCPUFA supplementation of formula during the first two postnatal months in healthy term infants does not alter neurological function at school age. The study confirmed that breastfed infants have a slightly better neurodevelopmental outcome than formula-fed infants.
2. *Cognitive and behavioural development:* The effect of postnatal nutrition on cognitive development largely depended on whether or not the mother had been smoking during pregnancy. In children exposed to smoking during pregnancy LF was associated with higher scores on verbal IQ and learning and memory (thereby largely reducing the substantial negative effect of maternal smoking on IQ); in children not exposed to smoking during pregnancy LF was associated with lower scores on IQ and verbal memory. The LF group scored worse than the CF group on executive function. Breastfeeding was associated with better performance on IQ, learning and memory and sustained attention and with less internalizing behaviour. We thus concluded that the effect of LCPUFA supplementation of formula in term infants is determined by maternal smoking during pregnancy. The study confirmed that breastfeeding is associated with better cognition – also when maternal IQ was taken into account.
3. *Cardiovascular and anthropometric development:* Heart rate, systolic and diastolic blood pressure and anthropometrics were similar in the two formula groups. Breastfed children had a lower heart rate than formula fed children, in particular compared to children fed control formula. Blood pressure and parameters of growth including body mass index of breast and formula fed children did not differ. We concluded that short term LCPUFA supplementation does not influence cardiovascular and anthropometric development at the age of 9 years. The study supported the minor beneficial effect of breastfeeding on cardiovascular development.

Effect of prenatal fatty acid status

We used neonatal fatty acid status in the walls of the umbilical vessels as a marker of prenatal fatty acid status. Relationships between neonatal fatty acid status and the various outcome measures (neurological condition, cognition and behaviour, growth and cardiovascular status at 9) have largely been analysed, but the results seem biologically conflicting. What seems clear is that in term infants prenatal fatty acid status has a larger effect on outcome than 2 months of postnatal LCPUFA supplementation. During the next months an international team (EARNEST partners) will meet to try to understand the results. We expect to be able to publish at least 2 additional papers on the basis of these data.

Concluding remarks

Activity 1.3.1 of Earnest has generated a wealth of new data and insights.

1. The effect of 2 months of postnatal LCPUFA supplementation in term infants on neurodevelopmental outcome largely depends on maternal smoking during pregnancy. In children prenatally exposed to maternal smoking LCPUFA supplementation of formula is associated with improved cognitive development. In (the large majority of) children not exposed to maternal smoking, short term postnatal LCPUFA supplementation is associated with a minor negative effect on developmental outcome. Two months of postnatal LCPUFA supplementation did not affect neurological condition, behaviour, anthropometrics and parameters of cardiovascular health at 9 years.
2. Breastfeeding is consistently associated with a better outcome at 9 years. This holds true for neurological condition, cognitive outcome, behaviour, and heart rate and also when maternal IQ is taken into account.
3. Most likely, the effect of prenatal fatty acid status is larger than that of early postnatal fatty acid status. The precise nature of the relationships need to be determined.

Publications

1. Hadders-Algra M. Prenatal long-chain polyunsaturated fatty acid status: the importance of a balanced intake of docosahexaenoic acid and arachidonic acid. *J Perinat Med* 2008; 36: 101-9.
2. De Jong C, Kikkert HK, Fidler V, Hadders-Algra M. The Groningen LCPUFA-study: effect of postnatal long-chain polyunsaturated fatty acids in healthy term infants on neurological condition at 9 years. *Br J Nutr* 2010; 104: 566-72.
3. Hadders-Algra M. Prenatal and early postnatal supplementation with long-chain polyunsaturated fatty acids – neurodevelopmental considerations. *Am J Clin Nutr*, accepted for publication.
4. De Jong C, Kikkert HK, Fidler V, Hadders-Algra M. Effect of supplementation of infant formula with long-chain polyunsaturated fatty acids is largely determined by maternal smoking during pregnancy. Submitted for publication.
5. De Jong C, Boehm G, Kikkert HK, Hadders-Algra M. The Groningen LCPUFA study: No effect of short term postnatal long-chain polyunsaturated fatty acids in healthy term infants on cardiovascular and anthropometric development at 9. Submitted for publication.