Early behavior and development are influenced by the n-6 and n-3 status in prematures

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Abstract: In a cohort of premature infants, consecutively included in the study at birth and followed to 18 months of age, the neonatal status of essential fatty acids and long-chain polyunsaturated fatty acids (LCPUFA) were investigated and correlated to the development at 40 and 44 weeks gestational age and at 3, 6, 10 and 18 months corrected age. The diet reported by the mothers contained low EFA, 98% had an intake < 1 energy% of n-3 fatty acids. Fatty acid analyses were performed in early breast milk and in mothers’ and infants’ plasma phospholipids early after birth and at gestational age 40 and 44 weeks. The development of the infants were assessed with Brazelton Neonatal Behavioral Assessment Scale (BNBAS) at 40 and 44 weeks and with Bayley’s Scales of Infant Development (Second Edition (BSID-II)) at 3, 6, 10 and 18 months corrected age. At 40 weeks and 3 months videotapes were made of the infants’ spontaneous motor behavior to assess the quality of their general movements. Adjustments for confounding background factors were made in multiple logistic regression analyses and mothers’ education had the highest impact of the background variables. At all ages tested the n-6 fatty acid concentrations, expressed as total concentrations, LA, AA or as ratios to n-3 fatty acids in breast milk and early plasma phospholipids were negatively associated with development. Positive associations with LCPUFA, especially DHA, were mainly found after 10 months of age. Both mental and motor developments had similar pattern of associations, fatty acid concentrations and background factors explaining 20-50% (R²) of the developmental scores. This was only an observational study, and it cannot be excluded that the highly negative influence of n-6 fatty acids was an effect of the low intake of n-3 fatty acids, which in the context of the changes generally seen in Western diet imply urgent need for larger studies.

Key words: arachidonic acid, docosahexaenoic acid, linoleic acid, mental development, motor development, orientation

Retrospective epidemiological studies have indicated the importance of adequate nutrition during fetal and early postnatal periods for later health and for the development of especially cardiovascular diseases, obesity and diabetes in the adults (Forsdahl, 1977; Barker et al., 1986; Eriksson et al., 2003). Animal studies have confirmed the influence of general and specific under-and overnutrition on later metabolism by programing during special sensitive periods of early life (Langley-Evans, 2004; Korotkova et al., 2005; Tamashiro and Moran 2010; Sebert et al., 2011). An increasing number of studies have now started to find mechanisms for this influence, by studying different epigenetic mechanisms both in humans, exposed to the Dutch famine during the Second World War (Tobi et al., 2009), and in animal studies (Waterland and Michels, 2007). Prospective studies from early life in humans are hitherto relatively rare. Most studies during the latest decades have focused on supplementation with long-chain polyunsaturated fatty acids (LCPUFA) during pregnancy and/or lactation for the neurological development, recognizing the difference in the supply of these fatty acids between formula and breast feeding, but without consideration of the great variation of fatty acids in breast milk. Few observational studies have investigated the habitual intake of nutrients in relation to ordinary development.

We have been interested in the observation that late premature with an uneventful history often have minor developmental differences later during childhood compared to those born at full term (Raju, 2006). The brain development is requiring a large surge for

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LCPUFA during the last trimester and early postnatal period, which is supplied by efficient intrauterine transport via the placenta and by the breast milk, which is especially providing docosahexaenoic acid (DHA 22:6n-3) (Sabel et al., 2009). At premature delivery this supply is abruptly discontinued, especially if mother’s milk is not available.

We hypothesized that premature delivery might by changes in fatty acid pattern influence the later development and therefore invited mothers delivering preterm infants to participate in an observational prospective study. The mothers, delivering at a community urban hospital, were included consecutively during 10 months. Fifty-one mothers and their infants were included, gestational age 25-36.9 weeks, mean (SD) 33 (2.6) weeks, with 75% of the infants being late prematures, born between 32 and 36 weeks, and 57% between 34-36.9 weeks. Mother’s mean age was 29.8 (6.0) years and BMI 24.9 (3.9) kg/m². In 52% the birth weight of the infants were >2000 g and mean birth weight was 2010 (590) g. Infants with malformation or those needing intensive neonatal care were not included, like mothers with chronic diseases. Extensive characterization of the mothers and infants have been presented (Sabel et al., 2009), and those data were used as confounding factors in the analyses.

Mother’s diet was registered for 3 days and mean fat intake was 31 (6) energy%, but the essential fatty acid intake was generally low, being <3 energy% in 33% of the mothers and 98% had n-3 fatty acid intake less than 1 energy% (Sabel et al., 2009). Breast milk was analysed at one week and plasma phospholipid fatty acid pattern in cord blood and in mothers and infants at one week, and at 40 and 44 weeks gestational age. The infants were examined for General movements (GM) at 40 weeks and 3 months (Hadders-Algra, 2001), with Brazelton Neonatal Behavioral Assessment Scale (Brazelton and Nugents, 1995) at 40 and 44 weeks, with the Selfregulation Scale at 40 and 44 weeks (Lundqvist-Persson, 2000) and by Bayley’s Scales of Infant Development (Second Edition BSID-II) at 3, 6, 10 and 18 months (Bayley, 1993). The results were compared to the early fatty acid analyses and adjusted for confounding factors in mothers and infants.

There was a strong correlation between mothers’ fat intake and the intake of essential fatty acids [11], r = 0.69 (p < 0.001), reflecting both linoleic (18:2n-6, LA) and alpha-linolenic (18:3n-3, ALA) acids (figure 1). Mead acid (20:3n-9; ETA) was negatively related to LA both in mothers’ (r = –0.64, p < 0.001) and infant’s (r = –0.37, p = 0.016) plasma.

In the premature infants LA increased by age and its corresponding LCPUFA, arachidonic acid (20:4n-6, AA) decreased (figure 2), illustrating a strong inverse association between these fatty acids in infants’ early plasma phospholipids (r = 0.90, p < 0.001), stronger than for ALA to DHA (figure 3). This might be an unexpected finding since the LCPUFA, including arachidonic acid is considered favoured in breast milk secretion. Our finding is in agreement with the pattern found in cells and plasma of adults, i.e. that high linoleic acid is associated with low arachidonic acid (Spector et al., 1981; Liou and Innis, 2009; Friesen and Innis, 2010). The finding, if confirmed, might be of concern in view of the high intake of LA generally in food and the importance of arachidonic acid for the early development (Schuchardt et al., 2010).

The DHA concentration in the infants’ plasma phospholipid was relatively constant in the breast fed infants to 44 weeks of gestational age but declined significantly in the mothers. The opposite patterns was found in infants and mothers not fully breast fed or lactating at 40 and 44 weeks of gestation (Sabel et al., 2009).

Similarly the ratio of n-6/n-3 fatty acids in infants’ plasma phospholipids were constant in breastfed infants to 44 weeks of gestational age, but showed a remarkable increase from 8 to 12 in those exchanging to more and more formula during the corresponding time.

Figure 1. The relation between maternal fat energy percentage intake and the energy percentage intake of linoleic acid (18:2n-6) (left) and alpha-linolenic acid (18:3n-3) (right). Data from Sabel et al., 2009.
The GM quality at 40 weeks was inversely associated to the ratio n-6/n-3 in breast milk, and in multiple regression analysis to the LA/ALA ratio ($b = -0.64$, $p < 0.001$). GM quality was also negatively correlated to the ratio of ETA/AA in breast milk and in multiple regression analysis to the Mead acid concentration ($b = -0.51$, $p = 0.001$). Motor assessment according to BNBAS was in multiple regression analysis negatively correlated to the n-6/n-3 ratio in infants’ early plasma phospholipids ($b = -0.39$, $p = 0.016$) and to the AA/DHA ratio in infants plasma at 44 weeks ($b = -0.46$, $p = 0.016$). The only
positive correlation at that early age was found between autonomic stability (BNBAS) at 40 weeks and the P/S ratio ($\beta$-0.43, $p = 0.009$) and the w6 E n ($\beta$-0.84, $p = 0.001$) in mothers food intake. Positive association was also found between the change in autonomic stability between 40 and 44 weeks and the EPA concentration in infants plasma (Lundqvist-Persson et al., 2010). Girls progressed more than boys when comparing BNBAS testing at 40 and 44 weeks.

Similar pattern, i.e. negative associations between GM quality and BNBAS items and different measures of n-6 fatty acids, was found in the Bayleys’ Scales at 3 to 18 months of corrected age (Sabel et al. to be published). Positive association to DHA concentrations was only found in tests after 6 months of age and the strongest correlation was found to mental development at 18 months ($\beta$ 0.417 ($p = 0.004$), after adjustment for confounders $\beta$ 0.805, $p = 0.038$, $R^2 0.50$. Mothers’ education was the strongest influencing confounding factor in all analyses. About 20-50% of the developmental measures could be explained by the early essential fatty acid and LCPUFA concentrations adjusted for the confounding factors.

In summary, there was a consistent trend that high n-6 fatty acids in early life were negatively correlated to motor and mental development up to 18 months. Since the general intake of n-3 fatty acids in the mothers was very low, it cannot be excluded that the negative influence of n-6 fatty acids more reflected the imbalance between the essential fatty acids than a pure negative effect of the n-6 fatty acids. On the other hand the inverse relation between linoleic and arachidonic acids might be of concern since arachidonic acid is important for early brain development (Schuchardt et al., 2010). The expected positive influence of DHA was first seen after 6 months of age. Our results have to be confirmed in larger studies in both premature and term infants, also in view of the relatively high ratio of n-6/n-3 fatty acids in formula, which might be necessary to reconsider.

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