Single nucleotide polymorphisms in desaturases genes – effect on docosahexaenoic acid levels in maternal and fetal tissues and early development of the child

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ABSTRACT

Polyunsaturated fatty acids (PUFAs) beneficially affect an optimal fetal growth and development right after birth. This effect is particularly significant for the growth and maturation of brain. Therefore, an appropriate maternal regimen for PUFAs supplementation, during pregnancy and lactation, may influence birth outcome and infant health. Recently, it has been shown that genetic profile is another factor determining long-chain polyunsaturated fatty acids (LC-PUFA) composition in human tissues. Single Nucleotide Polymorphisms (SNPs) in the fatty desaturase 1 and 2 (FADS1 and FADS2) modify endogenous synthesis of PUFAs indicating that PUFAs blood concentration may depend on genetic background. What is more, a number of studies indicate that maternal FADS gene variants by their influence on LC-PUFAs synthesis are associated with child’s health right after birth as well as within first years of life. Determining individual dietary recommendations for clinical practice can be beneficial for both mother and the child.

Keywords: pregnancy, supplementation, infant, FADS1, FADS2.

Introduction

Polyunsaturated fatty acids (PUFAs) play an important role including maintaining the fluidity of cell membranes and acting as precursors of eicosanoids, for example prostaglandins or thromboxanes, which are involved in inflammatory process. In addition, it has been shown that omega-3 fatty acids, among other properties like cholesterol-lowering and protective against the development of diabetes, cardiovascular pathologies, exhibits the essential role in proper development of the brain [1]. In neonates, particularly DHA is essential for the proper development of retina and nervous system, which is reflected by the accumulation of DHA in a fetus in the brain and the retina, especially during the 3 trimester of pregnancy and up to 2 years of age [2].

There are two main groups of PUFAs: omega-6 fatty acids, including linoleic acid (LA) (C18: 2, n-6), γ-linolenic acid (GLA) (C18: 3, n-6), arachidonic acid (ARA) (C20: 4, n-6). And omega-3 fatty acids, among which we distinguish α-linolenic acid (ALA) (C18: 3, n-3), eicosapentaenoic acid (EPA) (C20: 5, n-3), docosahexaenoic acid (DHA) (C22: 6, n-3). Linoleic acid and α-linolenic acid are essential unsaturated fatty acids because the human body does not have the proper enzymes to synthesize them. On the other hand, if these two acids are delivered in the right amount, it is possible to convert them into other PUFAs (Figure 1). From α-linolenic acid, eicosapentaenoic acid and
docosahexaenoic acid are produced, whereas arachidonic acid and γ-linolenic acid are produced from linoleic acid.

Human ability to synthesize the LC-PUFAs depends on FADS1 and FADS2 genes, deposited on chromosome 11 (11q12-Q13.1) respectively encoding the Δ5-desaturase (D5D) and the Δ6-desaturase (D6D) [3]. Although both genes are expressed in most tissues, the highest level thereof is observed in the liver [4].

Both omega-3 fatty acids and omega-6 are metabolized by the same pathway of desaturation and elongation, resulting in competition between the two families, particularly at the Δ5-desaturase, which converts linoleic and linolenic acid respectively to 18:3n-6 [3]. Interestingly, women have a greater ability than men to synthesize DHA from their precursors, which can be explained by the effect of estrogen on increasing the activity of Δ6-desaturase [5]. The purpose of this article is to review the study of single nucleotide polymorphisms in desaturase genes, their effects on DHA levels in blood and other tissues of pregnant women, in relation to the development and health of the newborn and child.

Single nucleotide polymorphisms in the FADS gene cluster

In 2006 a first genetic study demonstrating the relationship between plasma phospholipid composition and single nucleotide polymorphism in FADS genes has emerged. It appeared, that the minor allele carriers have a reduced ability to convert omega-3 and omega-6 fatty acids into their long chain products [6]. Studies of mothers and neonates under physiological conditions without supplementation of DHA showed a strong inverse relationship between the minor alleles for two desaturase SNPs and concentration of DHA and eicosapentaenoic acid (EPA) [2, 7]. Variants rs1535 and rs174575 FADS2 impact on a lower concentration of polyunsaturated fatty acids of both the maternal blood and umbilical cord blood [7]. It has also been found that SNPs in the FADS gene have a stronger effect on omega-6 fatty acids, resulting in an increase in linoleic acid levels and decrease in arachidonic acid in minor allele carriers. FADS gene polymorphism can explain 29% of the variance of arachidonic acid [2].

FADS1 and FADS2 genes, encoding the Δ5-desaturase (D5D) and the Δ6-desaturase (D6D), which play a major role in the desaturation and the elongation pathway n-6 and n-3 LC-PUFA, have been mapped in 2000 on chromosome 11q12-13.1. These two genes are located close together and with gene third desaturase FADS3 form together FADS gene cluster [8]. Over the past few years, scientists increasingly began to pay attention to the relationship between the occurrence of different allelic variants of these genes, the degree of activity of this particular desaturases and the same content in the tissues of the substrates and products of their activities [4, 8]. At least a dozen polymorphisms have been identified that may have a different effect. They can be located both in the noncoding regions, ie. 5’UTR, 3’UTR, introns or gene promoter and in coding regions [4]. Table 1 shows 13 discovered and investigated alleles.

All of them except rs498793 and rs526126 are significantly associated with higher levels of linoleic acid C18:2, n-6 and five of them (rs174546, rs968567, rs174572, rs174589, and rs174611) are associated with a higher C20:3, n-6 acid level. Minor alleles of all SNPs except one – rs498793 cause reduction of the level of arachidonic acid. Also, three SNPs (rs174546, rs174572, rs174589) are associated with significantly lower levels of eicosapentaenoic acid (C20:5 n-3). All haplotypes containing rs174546 minor allele showed a lower activity of Δ5-desaturase, and rs968567 minor allele was associated with a higher activity of the Δ4-desaturase [4]. However, another study showed that the polymorphisms may also favorably influence the activity of the desaturases and thereby increase the level of LC-PUFAs. Alleles rs3834458 and rs1535 are responsible for higher levels of DHA and EPA. This is due to increased activity of the enzyme in the last stage of the synthesis of long chain fatty acid products [3].

In order to show the importance of the effect of single nucleotide polymorphism of the amount of DHA there was also conducted a study comparing the con-

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concentration of fatty acids and their long-chain products, including DHA in the mother’s milk and their genotype. In women with rs174553, rs174583, rs99780, rs174575 minor alleles level of DHA as well as EPA or ARA was reduced compared with women without polymorphism [9], as seen in Table 2.

The effects of single nucleotide polymorphism in the FADS gene cluster are very important examples of interactions between genotypes, nutrition and their effects on the phenotype. Research indicates that FADS genotype is associated with the occurrence of various diseases, especially in children, which may be due to different amounts of polyunsaturated fatty acids, transported from the mother, whether it be through the placenta during pregnancy or after birth with milk [9].

**DHA intake during pregnancy and lactation – SNPs effect on DHA levels**

The dietary sources of omega-3 fatty acids in the diet include fish, walnuts, linseed oil, rapeseed, almonds and algae, while the main source of omega-6 are vegetable oils, such as soybean, sunflower, grape seed, corn, peanut, sesame oil [10]. Omega-3 and omega-6 fatty acids source may also be eggs, but their ratio and concentration depend on the way the hens are fed [11].

As already mentioned, consumed omega-3 and omega-6 fatty acids such as linoleic acid and α-linolenic acid must first be converted to their long chain products in the pathway shown in Figure 1. It is therefore preferable to consume direct sources of docosahexaenoic acid such as fish- mackerel, cod, salmon, herring, sole, but also algae and oil from them [10, 12].

During pregnancy and lactation, EPA, DHA, ARA and their precursors are transported from mother to child, respectively, by placenta or with mother’s milk, to provide an optimal growth, the development of the nervous and immune system or visual acuity [9]. Numerous studies indicate that during pregnancy and lactation, DHA intake should be at least 200 mg per day. This demand can be covered by the consumption of 1–2 servings of fish per week or by taking supplements containing DHA in the case of low consumption of dietary sources of fatty acids [5, 13]. Recently, the role of endogenous synthesis of long chain products of omega-3 and omega-6 acids by the enzymes called desaturases has also been noted.

In a study of pregnant women who consume fish, it was demonstrated that the level of DHA (approx. 7% erythrocyte FA) and AA was significantly lower in the third trimester of pregnancy until the birth of a child. Furthermore, this correlated with an increase in the concentration of these acids in the umbilical cord, which indicates increased transport to the fetus. On the other hand, mothers who did not eat fish or very small amounts, have DHA level in erythrocytes significantly lower.
dantly lower (about 2% FA) and did not change during pregnancy. However, to provide the necessary DHA for the baby, a compensatory increase conversion of ALA to DHA [15]. It was also pointed out that low fish consumption during pregnancy has been associated with delayed cognitive development of the child unlike the development of children whose mothers ate large amounts of fish, ran efficiently and effectively [5, 16]. Hibbeln et. al. have asked nearly 12,000 pregnant women to complete a survey on the amount of seafood consumed. Then, among children aged 6 months and 8 years, factors such as intelligence, communication skills and motor skills were compared. Results showed that the lower consumption of fish during pregnancy, the worse results obtained by the child [16].

Moreover it has been shown that a high consumption of fish and thus higher DHA supply may decline the genetic effect of SNPs on endogenous synthesis of this fatty acid. It was confirmed by a study on a group of pregnant women, living in Seychelles and consuming large amounts of fish. Yeates et.al. studied the effect of the FADS genotype on DHA and other blood fatty acids. This study showed that the rs3834458 genotype was associated with a 20% lower blood arachidonic acid level and a 42% higher LA: AA ratio, but no change in EPA or DHA levels was observed, which may be due to high intake of these fatty acids [17].

Some studies analyzed the relationship between consumption of fish rich in DHA by the mother and birth weight of the child. Most of them showed a positive correlation, which means a positive effect of LC-PUFA on the duration of pregnancy and fetal weight gain. Consumption of the DHA in excess of 200 mg per day, compared to consuming barely 34 mg results in an increase in birth weights, on average about 28g. In addition, also maternal genotype and SNPs occurring in desaturase genes are related to birth weight. Mothers who are homozygous for the minor allele (eg. FADS1 rs174556) gave birth lighter children, and the child’s weight was not associated with a child’s genotype [18]. Also mothers who are homozygous for rs174602 in FADS2 gene have children with lower weight, which is associated with lower levels of DHA because of the lower activity of Δ5-desaturase, controlling important step in the conversion of n-3 EPA to DHA [19]. In one study also noted the interaction between the consumption of AA and DHA and genotype – maternal intake of DHA increased the weight of the infant, whereas consumption of AA decreased the weight, but only in women who are homozygous for the minor allele [18].

Consumption of a large amount of DHA, or taking supplements can result in prevention of preterm birth, allowing a longer intrauterine fetal growth and higher birth weight [18]. This was also noted in a study where women were supplemented with 800 or 600 mg DHA/day or placebo [20]. The pre-term pregnancy rate in women taking DHA was 1.3% compared to 2.22% in the placebo group. Thus, consumption of foods rich in DHA or supplementation of this fatty acid can reduce significantly the risk of too low birthweight and preterm birth [18–20].

The level of LC-PUFA in the human milk vary according to the SNPs in the desaturase genes. Homozygous for the minor allele rs174553, rs174583 or rs99780 have much lower levels in milk ARA, EPA, DHA and higher 20:2 n-6 due to the lower activity of the Δ5-desaturase and Δ6-desaturase which are present also in the mammary gland. This is very disadvantageous for the newborn baby for which the DHA contained in breast milk is essential for the normal development of the nervous system. Studies have shown better development of the nervous system and the vision in infants fed with milk containing > 0.32g compared to those fed 0.2 g DHA / 100 g fatty acids [9]. Another study analyzed the relationship between genetic variants of FADS1 and FADS2 and the content of LC-PUFA in the mother’s colostrum. Most of these polymorphisms have adverse effects and cause lower blood levels of DHA, EPA, AA. The variants of rs174537, rs174570, rs2072114, rs174602, rs526126, rs174626, rs174464 and rs174468, which are associated with significantly lower AA content, have been detected here. Minor alleles rs174602 and rs174464 are clearly associated with a lower content of DHA in the blood, while the other showed the same direction at a concentration of DHA, as in the case of AA [14].

**DHA supplementation and SNPs in FADS gene cluster – pregnancy outcomes and newborn health**

As mentioned before, studies has showed that high consumption or supplementation of pregnant women with DHA can result in better pregnancy effects and can impact child development. Maintaining the adequate balance of DHA in the mother’s and the child’s tissues can be done by proper nutrition or supplementation of this fatty acid [12]. Unfortunately it is demonstrated that among Polish women aged 19–30 years, the average DHA intake was 110 mg, and among women aged 31–50 years – 120 mg, which does not cover
the minimum dose of 200 mg per day recommended by the Institute of Nutrition and Food [21], what may cause concern for the proper development of newborn babies. It was confirmed that supplementation of 200 mg DHA for 4 months after birth by mother results in up to 75% higher concentration in milk [22]. Especially in relation to the decreasing consumption of fish, eg. in the Nordic countries [5], it should be taken care of appropriate supplementation of this compound to provide the opportunity for your child to a suitable, undisturbed development and avoid the risk of various disorders in the future.

The rapid development of the brain (brain growth spurt) takes place predominantly in the 3rd trimester of pregnancy and during first year of age [13, 14], when the LC-PUFA are delivered from mother, first are transported through the placenta, then from breast milk. The greater part of the dry weight of the brain are lipids, of which 35% are long chain products of fatty acids [14]. LC-PUFA during fetal and early postnatal life are involved in the formation of the structure of cell membranes of neurons, myelination and in production of neurotransmitters such as dopamine or serotonin [13, 14]. In addition, DHA may affect the regulation of gene expression in the brain and participate in the processes of learning and memory, as it take part in the development of pre- and postsynaptic proteins involved in the transmission [13].

Therefore it was not surprising that children of pregnant women whose diet is deficient in LC-PUFA, consume little fish or are not supplemented with DHA showed delayed development, characterized by a lower level of IQ and poorer communication skills [13]. Colombo et.al. demonstrated that infants at the age of 4,6,9 and 12 months whose mothers was supplemented with DHA in an amount of 600 mg per day, could be more focused and better maintain attention compared to children of placebo-treated women. Moreover, the same study showed a positive correlation between supplementation and weight of the child (average difference approximately 360g) and head circumference (difference of approx. 1.5cm) [23]. This confirms the positive correlation between DHA supplementation and neonatal development what many studies confirmed.

Numerous studies have examined the effects of DHA supplementation, FADS genotypes, and the impact on health and development of newborns and children in later years. Supplementation of EPA / DHA during both pregnancy and lactation has also been correlated positively with the contents of DHA in the maternal RBC phospholipids [5]. In a study conducted in the United States, women who were homozygous for the minor allele of rs174533 FADS1 had lower levels of AA and DHA in the blood, whereas it increased significantly after supplementation with 600 mg of DHA during the last two trimesters of pregnancy [19]. This has been confirmed by research showing that the effect of FADS genotype also becomes less important in the case of fish oil supplementation, among those who had low levels of DHA in the blood at the beginning [17].

In another study 96 women received placebo (soybean and corn oil), while 195 women received 600 mg DHA from algae, 3 capsules per day for the last 2 trimesters. The study showed that among women with rs174533 minor allele placebo-treated women had lower DHA levels than women with a major allele. However, in the DHA supplemented group the level of this fatty acid was not depended on the genotype, and were higher in both groups with minor and major allele, compared to placebo. In the same study the level of DHA and other fatty acids in the plasma of infants was measured. DHA content in the group of children whose mothers were supplemented was significantly higher in comparison to the control group. The concentration of DHA in the first group was 4.81 ± 1.12% of the total fatty acid content, while in the control group 3.57 ± 1.08% [24].

This was shown in the study of premature infants who was born less than 33 weeks of pregnancy in order to assess the impact of breastfeeding mothers DHA supplementation on visual development [25]. Some women received six capsules containing 500 mg of DHA per day, while women from the control sample received soybean oil capsules, not containing DHA. They tested then visual evoked potential (VEP) acuity in infants ages 2 and 4 months. They were significantly higher in children 4-month fed by mothers supplemented with DHA, whereas no difference was noted in the age of two months, which may be associated with different sensitivity to methods of measurement in these two age ranges. Interestingly, the changes were much more clearly marked in male infants [25].

The importance of a balance between DHA and AA is also emphasized. It is very important for the development of the nervous system and the immune system [17]. Detected unfavorable relationship between the ratio of n-6 / n-3 on both psychomotor development and communication skills at 20 months of age [17] indicates that the balance between AA and DHA is required to ensure optimal development of a child. Moreover, it has also been proven that supplementation DHA lowers the level of arachidonic acid in women with rs174533 and rs174575 minor alleles respective-
ly in FADS1 and FADS2 genes, whereas this does not occur in pregnant women with major variants of these alleles, which changes the ratio of DHA to ARA, but the physiological effects of these changes are not yet known [24].

Also significant is the effect of DHA supplementation during pregnancy and breastfeeding on the development of the infant’s immune system. In order to demonstrate the relationship, examined more than a hundred families were examined. At least one person from each family suffers from allergy [26]. Pregnant women received a supplement containing either EPA and DHA or placebo. The children were subjected to allergic tests at the ages of 3, 6, 12 and 24 months. The proportions of children’s blood fatty acids, chemokine and antibodies against diphtheria and tetanus were also analyzed. It has been shown that children of DHA-supplemented women had lower concentrations of IL-13 and CCL17, which are associated with the proliferation of Th2 cells, which favors the development of allergies [26]. The Th2 / Th1 lymphocyte ratio was also lowered. In addition, in children whose mothers did not have allergies and were supplemented with DHA, a stronger response to tetanus and diphtheria vaccine was demonstrated, and higher levels of antibody in the blood against these pathogens, showing that supplementation can enhance the child’s immunity from birth and prevent to some degree development of allergy [26].

Another aspect is the duration of pregnancy. Women who are homozygous with the minor allele have a tendency to significantly shorter pregnancy period. Supplementation and diet rich in DHA increase this time. Neither the mother nor the child’s genotype did not modify the association between maternal PUFA intake and the duration of pregnancy [18]. However, an inverse relationship was observed between the level of arachidonic acid and the length of pregnancy, which is associated with the production of larger quantities of arachidonic acid products, e.g. prostaglandin E₂ and prostaglandin F₂, which support uterine contractions [18], while n-3 PUFAs may delay the delivery by inhibiting the production of these compounds. Also in the case of low consumption of fish and seafood or absence of supplementation of DHA levels of these two fatty acids decline in the mother’s body, because of their transportation and use by the fetus [5]. This involves a greater risk of postpartum depression in the mother, which also has a negative impact on the mother-child relationship [5]. It is therefore important to maintain the adequate amount of DHA in the circulation of pregnant women by appropriate diet and possible supplementation, especially in case of presence adverse desaturase variants, which reduce the amount of DHA during pregnancy.

**DHA supplementation and effect of SNPs on disease occurrence in children**

Supplementation of LC-PUFA and their precursors, during pregnancy and lactation, and polymorphisms in D6D and D5D genes may also have a long-term effects on health and child development [6]. First aspect is the issue of the impact of LC-PUFA on the development of allergies in children. Differentiation of unsaturated fatty acids in the blood of children remains strongly dependent on the genotype of FADS [27]. Barman et al. studied the relation between the occurrence of SNPs in FADS1 and FADS2 genes, as well as in elongase gene (ELOVL), with the occurrence of allergies in children. Blood samples were taken at birth and then at 13 years old. Children, which showed the presence of rs102275 and rs174448 minor alleles, had lower levels of arachidonic acid, and increased levels of 20:3 n-6 acid, what reduce significantly the risk of atopic eczema, but not inhaled allergens. ELOVL polymorphism did not influence the occurrence of allergies [28]. This study indicates the significant role of LC-PUFA in the development of eczema, and showed that reduced activity of desaturases reduces this risk. In the study of children from Germany, the relationship between FADS variants and atopic eczema was also confirmed.

However, in another study, this relationship was not explicitly confirmed. In one of the tested groups in which were children from the Netherlands, no relationship was obtained between the occurrence of variation PUFA and eczema in children, what does not allowed to confirm the role of fatty acids as precursors of pro-inflammatory molecules taking part in the development of allergies [27]. However, among children from Germany, the relationship between FADS variants and atopic eczema was confirmed. These discrepancies indicate the need for further studies in the field that will demonstrate the link between FADS1 and FADS2 genotypes, PUFA differentiation and allergy in children.

Another important issue is the effect of mother’s DHA supplementation on the intelligence level of the child. A study of 2839 pairs of mother-child (8 years), indicated that lower level of arachidonic acid and docosahexaenoic acid is associated with lower IQ of the child. Lower DHA levels correlated with IQ decreased...
by 1.5 score. At the same time, with decreased DHA concentrations, the concentration of 22: 5n-6 and 22: 4n-6 acids increased, replacing DHA during its deficiency. However, this substitution impairs the growth of axons and formation of synapses [29]. The lower level of arachidonic acid and the lower IQ at its deficiency may be associated with changes in the production of eicosanoids, which leads to a reduced electrical activity in the brain and the immune response. Also another study showed the relationship between supplementation and the level of IQ of the child (4 years). It was performed among randomly selected women who were supplemented from 18 weeks of gestation to 3 months after delivery of 10ml of cod liver oil or received placebo - corn oil. Children of mothers who had been taking DHA showed about 4 points higher IQ level [30].

According to the results obtained, SNPs in the mother’s desaturase genes exert a strong influence on fetal and infant fatty acid levels, and the DHA concentration in their tissues correlates with the amount of parental intake of the mother. However, according to one study, this effect disappears with age [7]. These contradictions indicate the need for further research in this field.

Summary

The existence of SNPs in FADS and their effect on the fatty acid composition in tissues has already been well established. It is certain that the presence of multiple variants of the alleles of desaturase genes modifies their activity and disturbs the balance of PUFAs and their long chain products in the body [7, 8, 14]. Ongoing researches try to discover new polymorphisms and FADS gene variants.

It is now known that DHA and other long-chain PUFAs – EPA and AA, play a very important role in the development of the fetus and newborn. Especially DHA is responsible for the proper functioning of such important organ as brain [2]. Therefore, it is important to supply the appropriate amount of this fatty acid initially through the placenta with the mother's blood and then with the breast milk. In addition, the increasing importance when it comes to providing DHA to the fetus and the baby during breast-feeding and for widely understood and proper development of the baby’s health, gaining the genetic background associated with the presence of different variants of desaturase genes. SNPs according to the locations in gene can variously modify the activity of these enzymes by changing the level of DHA or other LC-PUFA in the tissues of the mother and the child. The presence of polymorphisms has a significant impact on the process of endogenous synthesis DHA from precursors supplied with the diet. Attention is paid now to the relationship between the intake and supplementation of DHA and genetic background [24]. These are undoubtedly very important issues that will make a chance to ensure an optimal child development from the first days of intrauterine life.

However, there are also many questions about the relationship between the SNPs, the content of LC-PUFA and the occurrence of many diseases, such as allergies, diabetes, cardiovascular disease in different age groups. Studies on the impact of polymorphism often provide contradictory information, which is often also associated with the selection of the study group, their origin, age, environment, and also studied variants of the FADS gene alleles.

Furthermore, an interesting issue, although certainly far distant for the present, is if it would be possible to determine the genotype of FADS in women, so as to detect whether they are in a group having a minor alleles, which impair the pathway of endogenous production of DHA. It would allow to apply a correspondingly larger supplementation, to compensate for the lack of the endogenous synthesis and provide the appropriate development of the baby from the first weeks of intrauterine life. It is also interesting to note that supplementation with larger amounts of DHA can neutralize the negative effects of SNPs. Women who supplemented 600 mg of DHA and were the minor allele carriers had significantly higher levels of DHA in plasma compared to those taking placebo [24]. Therefore, supplementation of larger amounts than the recommended 200 mg can cause positive effects. Women at risk of premature labor should consume as much as 1000 milligrams a day, which can prevent them from miscarriage [31].

All this issues require numerous studies that will draw conclusions and discover facts that allow us to complete the knowledge about the importance and the role of fatty acids and their long chain products in human body and the effects of their disturbed equilibrium. They can also present wider range of very important place of genetics and genetic background in the regulation of many physiological processes..

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