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Case Report

Can 5-methyltetrahydrofolate modify the phospholipid fatty acid pattern in cystic fibrosis pediatric patients?

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Abstract

Recent studies have reported an imbalance between n6 and n3 fatty acids (AA and DHA) in subjects with CF. Alterations in fatty acid amounts are present in CFTR-expressing tissues, plasma and in circulating blood cells. It has been reported that the correction of polyunsaturated fatty acid deficiency reversed the organ pathologies observed in CF knockout mice.

We describe a CF child with an unusual clinical course presenting high molar percentage of DHA in plasma and red cells membrane during supplementation with 5-methyltetrahydrofolate and vitamin B12.

Keywords: Cystic fibrosis; 5-Methyltetrahydrofolate; Methylation; Phospholipid; Docosahexaenoic acid; Fatty acid

1. Introduction

The presence of a fatty acid defect is well known in subjects with cystic fibrosis (CF) mutations [1,2]. It has been suggested that fatty acid abnormalities could play an important role in the phenotypic expression of CF disease; in particular, it seems that administration of high doses of oral docosahexaenoic acid (DHA) in CF knockout mice may reverse the pathological changes observed in cystic fibrosis transmembrane conductance regulator (CFTR) regulated tissues [3].

Alterations in phospholipid fatty acid amounts are present in the plasma, red blood cells membrane and tissue expressing CFTR from CF patients [4,5]. Lower levels of linoleic acid and docosahexaenoic acid (DHA) have been reported even in CF patients with pancreatic sufficiency and adequate dietary intake [6]. Evidence for primary abnormalities in fatty acid metabolism in CF also includes the essential fatty acid deficiency in cord-blood phospholipids of CF newborns [7].

Here, we describe a CF child presenting high molar percentage of DHA in plasma and red cells membrane during supplementation with 5-methyltetrahydrofolate (5-MTHF).

2. Case report

The child was born at term and appeared healthy but the neonatal screening test was positive for CF (IRT was 143 μg/l), as also confirmed by the increased chloride level at the sweat test (88 mEq/kg). Genotype was investigated and two mutations in the CFTR gene were identified (deltaI507/4382delA). In the child's first 4 months of life the levels of chymotrypsin were low or borderline (3.35–1.8–4.8–2.6 U/g stool), but pancreatic enzyme replacement was not started because the child's growth weight was regular.

Supposing that changes in fatty acid composition could be induced by phospholipid methylation related to folic acid supplementation, as several studies suggest [8,9], we decided to investigate the effect of treatment with 5-MTHF on the phospholipid fatty acid pattern of plasma and red blood cell membranes in the CF child and in her mother.

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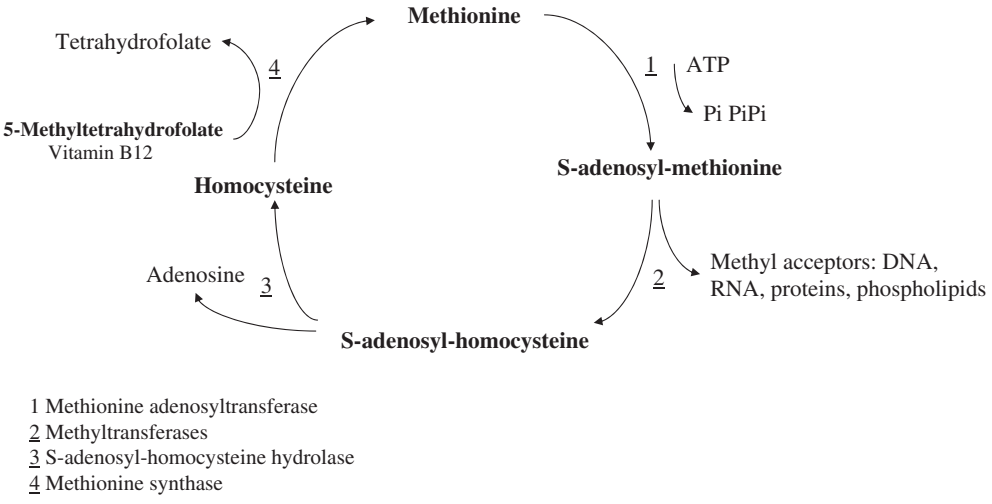

Fig. 1. Metabolic cycle of methionine.

Therefore, when the CF child was 2 months old, the mother began a daily supplementation of 15 mg of 5-MTHF and the subsequent dosage of folic acid in her milk was of 51.4 μg/ml. The child suckled about 400 ml per day, and 6 months later, plasma and red blood cell folate levels were respectively 92 ng/ml and 306 ng/ml for the mother and 51 ng/ml and 403 ng/ml for the child.

The plasma DHA level of the child increased during 5-MTHF supplementation from 1.62% to 3.16% and, surprisingly, it was higher than that observed in a healthy age-matched control child (1.96%). A higher relative molar percentage of DHA was also present in the erythrocyte membrane lipids of the CF child compared to the control, 8.94% and 5.98%, respectively. High values of plasma and erythrocyte DHA were reconfirmed later.

The mother's plasma DHA level also significantly increased during the 5-MTHF treatment from 1.75% to 2.62% and, similarly, the value of DHA in red blood cells membrane was higher than in a healthy control (6.16% vs. 5.3%).

Unfortunately, the storage of the red blood cells collected before treatment was inadequate and, therefore, it was not possible to carry out a comparison before and after treatment.

It has been 6 years since the beginning of the folic acid supplementation and 5-MTHF is presently given to the CF child at the dose of 30 mg per week; vitamin B12 has been added. During this period the child has been free from clinical or radiological lung disease and her growth rate has been normal without using pancreatic extract. Two months after the beginning of the treatment with 5-MTHF, stool chymotryptic activity appeared to be normal, increasing to higher levels at the following checks.

3. Discussion

This case prompts us to speculate that changes in fatty acid composition could be mediated by an increase of methionine bioavailability, which is 5-MTHF dependent. Methionine is necessary to guarantee sufficient S-adenosyl-methionine synthesis (Fig. 1). S-adenosylmethionine participates in most cellular transmethylation reactions including phosphatidylethanolamine (PE) methylation (Fig. 2). Phosphaditylcholine (PC) produced by this pathway is enriched in polyunsaturated fatty acids [9]. Recently, it has been demonstrated that the plasma PE/PC ratio is significantly higher in CF children than in control children whereas methionine is lower [10]. The disrupted methionine and phospholipid metabolism could explain the reduced levels of DHA in CF children, even if the reasons for this have still to be clarified.

Another study suggests the importance of methylation in CF patients, demonstrating that only methylated phospholipids appear to have an improving effect on mutant CFTR by increasing the expression of deltaF508 CFTR and promoting the expression of higher molecular weight CFTR forms [11]. Moreover, it has been proved that methylation in the promoter of the epithelial amiloride-sensitive Na

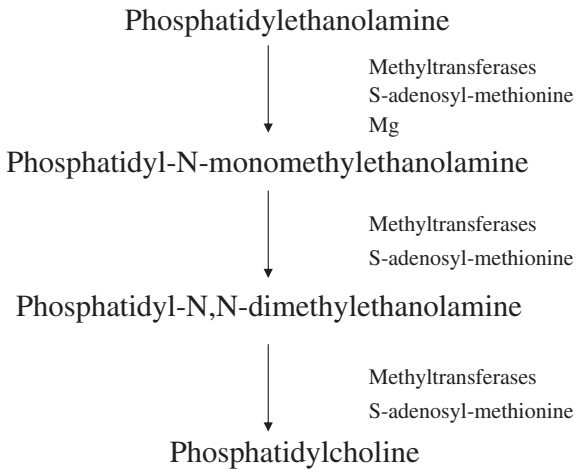

Fig. 2. Membrane phospholipid methylation.

channel gene inhibits the hyperactivity of this channel in human CF airway epithelia cells [12].

In conclusion, we suppose that changes in methylation may have pathophysiological significance for the CF clinical picture, as supported by the present case. We are planning further investigations on the effects of 5-MTHF supplementation to evaluate its possible clinical applications in CF patients.

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