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Omega-3 fatty acids as a psychotherapeutic agent for a pregnant schizophrenic patient

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Abstract

Because of the potential adverse events and teratogenesis of antipsychotic drugs, it is important to find a safe and effective treatment for pregnant women with severe mental illness. The membrane hypothesis of schizophrenia provides a rationale to treat symptoms of schizophrenia with omega-3 PUFAs. We report a 30-year-old married woman with chronic schizophrenia, who experienced an episode of acute exacerbation of psychotic symptoms during pregnancy. After entering into an open trial of omega-3 PUFAs monotherapy, she showed a dramatic improvement in both positive and negative symptoms of schizophrenia and a significant increase of omega-3 PUFA composition in erythrocyte membrane. There were no adverse effects in this treatment. Thus, omega-3 PUFAs could be both beneficial and therapeutic to pregnant schizophrenic women.

Keywords: Omega-3 polyunsaturated fatty acids (PUFAs); Pregnancy; Schizophrenia; Teratogenesis; Ecosapentaenoic acid (EPA); Docosahexaenoic acid (DHA)

1. Introduction

Because of teratogenesis and other adverse events in the fetus, avoidance of pregnancy and withholding of drug therapy during pregnancy are commonly suggested to minimize the risk of fetal drug exposure. However, these suggestions are not often possible in treating a pregnant woman who has a serious psychiatric illness. Once a decision to offer pharmacotherapy is made, the clinicians face lots of limitations and considerations, including efficacy of the drugs available, the anticipated response of the individual patient, and the overall toxicity profile of the drug for the mother and fetus (Committee on Drugs, American Academy of Pediatrics, 2000). Thus, to find a safe and effective pharmacotherapy for the severe psychiatrically ill pregnant women is clinically important.

The use of omega-3 polyunsaturated fatty acids (PUFAs) in pregnant women is increasingly common. The PUFAs are classified into two main groups, omega-3 (or n−3) and omega-6 (or n−6) families. The parent fatty acid of omega-3 family is alpha-linolenic acid (ALA; 18:3n−3), and that of n−6 family is linoleic acid (LA; 18:2n−6). Omega-3 PUFAs are found in plant and marine sources, such as marine-derived omega-3 PUFAs including high levels of ecosapentaenoic acid (EPA; 20:5n−3) and docosahexaenoic acid (DHA; 22:6n−3). Unlike saturated fatty acids, omega-3 PUFAs are found to have many health benefits in neonates and women in pregnancy and lactation. Recently, one preliminary double-blind, placebo-controlled trial (Stoll et al., 1999) seems to suggest the omega-3 PUFAs could improve the outcome, especially for the prevention of recurrent depression (Su et al., 2000a) in the bipolar patients. We therefore reviewed the effects of omega-3 PUFAs on psychiatric disorders (Su et al., 2000b): Horrobin et al. (1994) proposed membrane hypothesis of schizophrenia, which was supported by revealing the abnormalities of omega-3 PUFAs in the frontal cortex of the postmortem brain tissue (Horrobin et al., 1991) and red cell membrane (Yao et al., 1994), as well as an association between dietary omega-3 PUFAs intake and

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severity in schizophrenia (Mellor et al., 1996). These findings not only suggested a possible etiology for schizophrenia, but also give the rationale to treat schizophrenic patients with omega-3 PUFAs. Therefore, omega-3 PUFAs could be promising therapeutic alternatives for psychiatric patients during pregnancy and lactation (Freeman, 2000).

Here, we are reporting a case of unmedicated pregnant schizophrenic patient successfully treated with omega-3 PUFAs (EPA/DHA). The patient had a dramatic reduction in both positive and negative symptoms of schizophrenia and a significant change in red blood cell membrane omega-3 PUFA compositions.

2. Experimental procedures

2.1. Case report

Miss A, a 30-year-old married woman who came to our psychiatric service for her acute exacerbation of auditory/visual hallucinations, bizarre delusion and sleep/behavioural disturbance.

Since age 25 years, Miss A had persistent hallucinations and a complex delusional system, including when she was pregnant with her first child. Since she was 28 years old, the patient also has had obvious negative symptoms of schizophrenia, including anhedonia and social withdrawal. Due to stigma, her families deprived her of professional treatment. During the first trimester of this pregnancy, her psychotic symptoms and behavioural disturbance worsened, therefore, her obstetrician referred her to us for psychiatric care.

In mental status examination, Miss A looked anxious and agitated. She had vivid auditory/visual hallucinations and florid delusions. Her mood was depressed. Her speech was relevant and coherent, but her thought form was impaired. She was orientated to time, place and person. She had intact recent memory as shown in her ability to recall three objects in 5 min. The abilities in speech, language comprehension, and naming objects, were intact.

She had no history of substance abuse, or any medical or surgical condition that might account for her psychiatric symptoms. The Axis I diagnosis in DSM-IV (American Psychiatric Association, 1994) was schizophrenic disorder, paranoid type.

Miss A refused medication, but she and her husband gave written informed consent to enter into an open single-case trial with EPA/DHA. The patient received 4 g of EPA and 2 g of DHA per day. She was rated with the Positive and Negative Symptoms Scale (PANSS; Kay et al., 1987) 1 month before treatment and during the treatment until her delivery. The ratings were carried out biweekly for the first 2 months and then monthly for 6 months.

Miss A was also monitored for laboratory assessments of erythrocyte fatty acid compositions on week 0 (before EPA/DHA supplement) as well as weeks 4 and 8. The blood samples were obtained in the morning, 12 h after the evening dosing.

2.2. Fatty acids analysis of red blood cells

Blood samples were analyzed for individual fatty acids with gas chromatography of methyl esters. Individual fatty acids were identified by comparison of gas chromatography (Lipid Standards, FAMEs) (Sigma Co., St. Louis, MO, USA). The step-by-step procedures are described elsewhere (Edwards et al., 1998; Maes et al., 1999).

3. Results

Fig. 1 depicts that there had been no changes in the PANS S scores before omega-3 PUFA treatment (week 4 to week 0) and that the treatment with omega-3 PUFAs led to remarkable improvements in both positive and negative symptoms of schizophrenia between weeks 2 and 4. The improvement persisted from week 4 to the following months. She received haloperidol therapy after the delivery and her condition has continued to maintain stable.

Prior to treatment with omega-3 PUPA, the patient had abnormally low erythrocyte membrane levels of all the major long-chain omega-3 and omega-6 fatty acids. As shown in Table 1, omega-3 PUFA treatment produced a significant change of omega-3 PUFA compositions, omega-3/omega-6 ratios, and AA/EPA ratios in erythrocyte membrane.

4. Discussion

Miss A showed remarkable improvements in both positive and negative symptoms of schizophrenia after receiving omega-3 fatty acids. The results of this patient's mental status examination had remained unchanged for three previous years, and the clinical course showed no evidence of spontaneous remission or any episodic improvement of her illness. It is unlikely that the remission was a consequence of clinical attention of the regular follow-up visits, for the patient had received the same regular attention 4 weeks before she enrolled to this study.

The limitations of this study are the absence of the control group and the possibility of the placebo response. It is important to address that up to 50% of placebo response may be expected when a new or controversial medication is used regardless of prior history. These limitations could be improved in the future study by using placebo lead-in duration with blind rater or the double-blind controlled trial.

To date, no psychotropic drug has been approved to be safe during pregnancy. Psychiatrists are thus faced with a difficult task to make recommendations to prescribe psy-

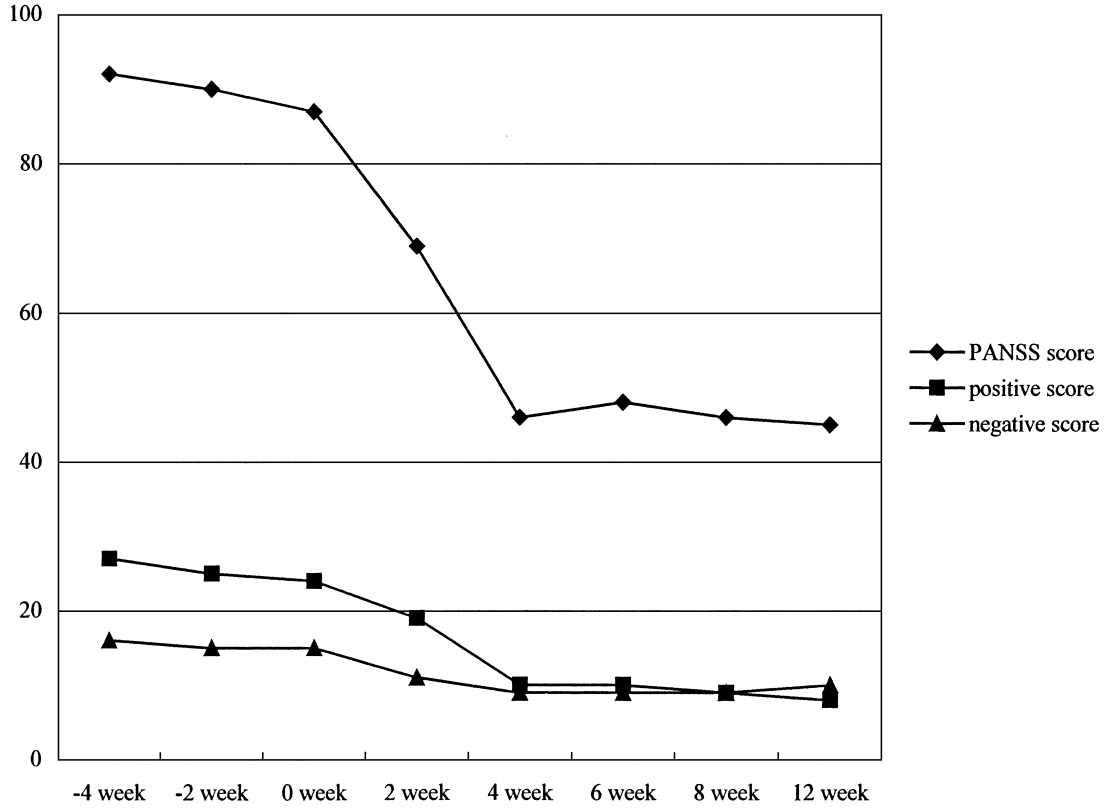

Fig. 1. Patient's Positive and Negative Symptoms Scale (PANSS) on 4 weeks (−4 weeks), 2 weeks (−2 weeks) before receiving omega-3 PUFAs; the beginning (0 week) and 2, 4, 6, 8 and 12 weeks after treatment.

chotropic drug for pregnant patients. Knowledge of risks of psychotropic medications to the fetus of prenatal exposure is incomplete. It is neither feasible nor ethical to design the prospective, case-control studies for the risks of psychotropic drugs to both mother and child during pregnancy. Thus, the appropriate data from observation studies and alternative, non-drug treatments are important.

Based on the data of lower levels of omega-3 PUFA compositions in red blood cells (Yao et al., 1994), brain (Horrobin et al., 1991) and cultured skin fibroblasts (Mahadik et al., 1996) in schizophrenic patients, the hypothesis of deficient uptake or excessive breakdown of membrane omega-3 PUFAs in schizophrenia is proposed (Horrobin et al., 1994). The results in the open trial of 'add-on' studies and one case report of monotherapy (Peet et al., 1996; Shah et al., 1998; Puri and Richardson, 1998; Richardson et al., 2000) revealed that the omega-3 fatty acids are associated with the improvement in the PANS S scores and the Abnormal Involuntary Movement Scale (AIMS; Guy, 1976). But the exact mechanism is unknown. One hypothesis is that omega-3 PUFAs actively inhibits cytosolic phosphlipase 2 (PLA_2) (Richardson et al., 2000; Gattaz et al., 1995; Ross et al., 1997). The other hypothesis is that the omega-3 PUFAs can normalize the altered membrane microstructure and neurotransmission of dopamine and serotonin (Malnoe et al., 1990; Delion et al., 1996). These may be the mechanisms, in addition to the receptor-blocking profile, to contribute to the therapeutic effect in schizophrenia (Horrobin, 1998).

The essential fatty acids (EFAs) of the omega-3 and omega-6 families play important roles during pregnancy. During pregnancy, accretion of maternal, placental and fetal tissue occurs and consequently the EFAs requirements are high. Furthermore, the fetal requirements for arachidonic acid (AA) and DHA are especially high in the last trimester of pregnancy because of the rapid synthesis of brain tissue (Clandinin et al., 1980; Martinez, 1992). DHA, for example, accumulates in the fetal brain three to five times more rapidly during the last 3 months of pregnancy than it does during the first months of gestation (Nettleton, 1993) for it performs many membrane functions in neuronal synapse and photoreceptor outer segments (Sastry, 1985). At birth, the infant's plasma contains more DHA and AA than mother's plasma does (Carnielli et al., 1996; Leaf et al., 1992).

Since omega-3 PUFAs are thought to be both beneficial and therapeutic to pregnant schizophrenic women, we are now conducting a double-blind controlled trial. Hopefully, the trial of omega-3 PUFAs may help shed some light on the pathophysiology of schizophrenia.

Table 1
Patient's lipid profiles (%) in acute and the following remitted stages after EPA/DHA monotherapy

	Pre Test (week 0)	Test 1 (week 4)	Test 2 (week 8)
SFA(%)			
16:0	15.86	7.99	8.44
18:0	4.87	4.47	5.73
MUFA (%)			
16:1	4.93	5.95	4.72
18:1	66.68	70.95	69.77
PUFA, n−3 (%)			
18:3	0.41	0.90	1.31
18:4	0.12	1.11	1.69
20:5 (EPA)	0.09	1.28	0.42
22:6 (DHA)	0.12	0.25	0.42
PUFA, n−6 (%)			
18:2	6.68	6.86	7.27
20:4 (AA)	0.07	0.23	0.25
Ratio (%)			
n−3/n−6	0.11	0.50	0.51
AA/EPA	0.78	0.18	0.59
PUFA/UFA	0.10	0.12	0.13
PUFA/SFA	0.37	0.85	0.80
PUFA/MUFA	0.11	0.14	0.15
MUFA/SFA	3.45	6.17	5.26
SFA/total (%)	20.73	12.46	14.17
PUFA/total (%)	7.67	10.64	11.34
MUFA/total (%)	71.61	76.90	74.49

SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; EPA, ecosapentaenoic acid; DHA, docosahexaenoic acid; AA, arachidonic acid.

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