Case report

Early dietary treatments with Lorenzo’s oil and docosahexaenoic acid for neurological development in a case with Zellweger syndrome

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Abstract

We treated a girl with Zellweger syndrome using a special infant formula supplemented with middle chain triglyceride (MCT) milk, docosahexaenoic acid (DHA), Lorenzo’s oil, and Lunaria oil, which is rich in nervonic acid (C24:1). We examined the fatty acid contents of the plasma and red blood cell (RBC) membrane. Neurological development was evaluated using Denver developmental screening test and auditory brainstem response (ABR). Her delayed neurological development, liver dysfunction, and cholestasis were all improved 2 weeks after starting the dietary treatment. DHA level in RBC membranes was increased and very long chain fatty acid (VLCFA,C26:0) levels were decreased. Our findings suggest that the dietary treatment with combination of MCT milk, DHA, Lorenzo’s oil, and Lunaria oil in the patients with Zellweger syndrome bring some benefits for neurological development.

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1. Introduction

Zellweger syndrome is a peroxisomal disease with a serious metabolic disorder of very long chain fatty acids (VLCFAs), leading to severe psychomotor retardation, retinopathy, liver disease, and early death. The lack of peroxisomes and their enzyme, affecting plasmalogen synthesis and β-oxidation of VLCFAs, is a characteristic finding of Zellweger syndrome. The main causes of multiple organ dysfunction and neural damage are caused by the defective peroxisomal β-oxidation, the decreased levels of docosahexaenoic acid (DHA) and accumulation of VLCFAs. It has been suggested that dietary treatment with DHA, n-3 polyunsaturated fatty acid (PUFA) and Lorenzo’s oil, long chain monounsaturated fatty acid (MUFA), supplementation is efficacious for Zellweger syndrome [1–5]. However, detailed nutritional and neurological evaluations with dietary treatments have not been performed.

The aim of the present study was to evaluate benefit of the dietary treatment, especially with DHA and Lunaria oil (a longer-chain MUFA than Lorenzo’s oil), in Zellweger syndrome. We examined serum and red blood cell (RBC) membrane fatty acid composition, neurological developments, and acoustic brain stem response, which revealed the level of myelination in the neural system. This is the first trial of Lunaria oil, rich in nervonic acid (C24:1), in Zellweger syndrome.

2. Methods

Dietary treatments, including supplementation with MCT milk, DHA (Fish oil; Incromeda DHA J27,
Croda, Japan, K/K, Tokyo Japan), Lorenzo’s oil, and Lunaria oils, which is rich in nervonic acid (C24:1), were performed after the diagnosis of Zellweger syndrome. Glycyrrhizin and taurin were also administered to treat liver dysfunction and cholestasis. The composition of the oils are showed in Table 1. We evaluated the fatty acid content, including VLCFA and DHA, of the plasma and the RBC membranes by gas chromatography. We also used Denver developmental screening test II, the auditory brainstem response (ABR) and electroencephalography (EEG) for evaluation of the patient’s clinical neurological development Table 2.

3. Case report

The patient was born with a body weight of 1668 g at 38 weeks of gestation as the second baby of unrelated healthy parents. She had asphyxia, hypotonia, and mild liver dysfunction with cholestasis at birth. She was on mechanical ventilation for survival soon after birth, because of her weak spontaneous respiration, which was due to poor muscle tone.

The cholestasis and floppy condition became prominent, and she developed generalized convulsions with worsening liver function tests including serum total bile acid level. We diagnosed classical Zellweger syndrome based on following findings, high serum levels of VLCFA and phytic acid, non-ketotic dicalbouremia, and the lack of peroxisome in the fibroblast on skin biopsy. And she had no known gene mutation previously reported”.

After diagnosis, we started treating the patient with MCT milk on day 40, Lorenzo’s oil and DHA on day 55. The DHA level in RBC membranes increased after the treatment. Plasma VLCFA (C26:0) levels were 2.4, 1.4, and 2.0 mg/ml on day 35, 60, and 90, respectively. Liver function and cholestasis were also improved. The patient’s behavior and state of arousal improved, and she showed social smiling on day 60. Her muscle tone and strength improved significantly, such that she could wean herself from mechanical ventilation after three weeks of treatment. On neurological examination, she started to show eye-to-eye contact and horizontal excursion was sufficient to follow a moving ring. She also started to inspect her surroundings and to respond to the sound of a rattle. No convulsions developed after the treatment. Although she showed no ABR on 7 days of age, a response emerged on day 80.

Initially she did not require a nasogastric tube for feeding, due to increased power of oral sucking. Moreover, the VLCFA level was significantly decreased to 1.5 g/ml on day 130 after we started treatment with Lunaria oil, which is rich in nervonic acid on the fatty acid composition, on day 112 (Fig. 1). However she developed recurrent pneumonia and gastro-intestinal bleeding due to cholestasis. Gradually her muscle tone and emotional change were diminished even though biochemically improved.

She died on day 144 due to liver failure and disseminated intravascular coagulopathy followed by sepsis”.

With the patient’s parents consents, we measured the levels of VLCFA and DHA in her organs after death. The results revealed that VLCFA was significantly decreased in the organs and DHA was increased in the frontal cortex, liver and kidney, compared with the patient with Zellweger syndrome previously reported by Martinez [6] (Table 2).

4. Discussion

In this study, we demonstrated that early dietary treatment with a combination of Lorenzo’s oil, Lunaria oil, and DHA can alleviate multiple organ damages and improve neurological development in a patient with classical Zellweger syndrome. These results suggest that administration of long chain MUFA (Lorenzo’s oil and Lunaria oil) was effective in decreasing the accumulation

<table>
<thead>
<tr>
<th>Case</th>
<th>Lipid</th>
<th>VLCFA (nmols/g of wet tissue)</th>
<th>DHA (nmols/g of wet tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Frontal cortex</td>
<td>Liver</td>
</tr>
<tr>
<td>Present case</td>
<td>15</td>
<td>40</td>
<td>132</td>
</tr>
<tr>
<td>Reported case</td>
<td>12</td>
<td>72</td>
<td>305</td>
</tr>
<tr>
<td>Control n = 5 mean ± SD</td>
<td>33 ± 21</td>
<td>29 ± 6</td>
<td>28 ± 5</td>
</tr>
</tbody>
</table>

Present case, the results from dissection of the patient’s body; reported case, a Zellweger syndrome in the report by Martinez et al. 1991; control, five healthy controls in the report by Martinez 1989.
of VLCFA. In particular, this is the first report of showing the efficacy of Lunaria oil for the patient with Zellweger syndrome. This oil has been reported before its efficacy and safety to animal experiment. One of the minor side effect that mild thrombocytopenia of peripheral blood [7], however there was no apparent side effect in this case.

The mechanism of this effects are considered that the elongation of fatty acid is synthesized by the same enzyme elongase, administration of Lunaria oil, which was contained high level of C18:1/C20:1, can promote production of LCPUFA (C26:1) under the use of elongase. Since same elongase producing C26:0/VLCFA, consumption of elongase LCPUFA production reduce the total amount of C26:0 production which may lead to maintain brain damage as well as other organ failure. Also alleviates neurological damage by administered DHA because DHA plays a important role of myelination during infancy.

Moreover, we have confirmed that supplying DHA oil could increase the DHA level in the brain. Since DHA has an important role the development of myelination in the brain during early infancy, our results suggest that it is essential to initiate this treatment soon after diagnosis.

Martinez et al. confirmed the dramatic effects on neurodevelopment, evaluated by magnetic resonance imaging and clinical evaluation, of increased levels of DHA after DHA therapy in the patients with Zellweger-like syndrome [1,4,8]. DHA administration may be useful to make the high level of DHA blood concentration, because DHA is synthesized in peroxisome [9]. Also middle chain fatty acids metabolism may be of great advantage to disuse peroxisome. And we guess our combination therapy may be effective in an early infants as middle chain fatty acid catalysis and β-oxidation ratio changes developmentally [10]. Also Suzuki et al have reported that the effects of DHA therapy for the neurological development to the patient with peroxisome biogenesis defect with mild phenotypes [11]. However, these patients did not have classical Zellweger syndrome. Thus, the present study is the first trial to evaluate a patient with classical Zellweger syndrome, which is the most severe of the generalized peroxisomal disorders. Our data suggest the administration of Lunaria oil with Lorenzo’s oil could lower VLCFA levels. It is also suggest that supplementation with DHA could increase DHA levels in the brain, leading to improved neurological development and ABR findings in patients with classical Zellweger syndrome.

Our findings suggest that dietary treatment with MCT milk, Lorenzo’s oil, Lunaria oil, and DHA in patients with Zellweger syndrome bring the benefits in both biochemically and neurologically. Without this combined dietary treatment, restoration of brain DHA levels and prevention of further organ damage will not occur. Further evaluation of this dietary combination treatment for classical Zellweger syndrome is needed.

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References


