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Short Communication

Oral Ether Lipid Therapy in Patients with Peroxisomal Disorders

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Peroxisomes are catalase-containing subcellular organelles which play a role in lipid metabolism. Patients with peroxisomal disorders lack the membrane-bound peroxisomal enzyme, dihydroxyacetonephosphate acyltransferase (DHAP-AT), which catalyses the first step in the biosynthesis of plasmalogens (Datta *et al.*, 1984; Schutgens *et al.*, 1984). However, the distal enzymes of plasmalogen synthesis have significant activity in fibroblasts of patients with Zellweger syndrome (Schrakamp *et al.*, 1985) and incorporation of alkylglycerols into plasmalogens proceeds normally in these fibroblasts. Since dietary 1-alkylglycerols are absorbed intact (Blomstrand, 1959), dietary supplementation with plasmalogen precursors offers potential therapy for treating patients with peroxisomal disorders. We present the results of administering alkylglycerols to two patients with decreased DHAP-AT activity and low levels of erythrocyte plasmalogens.

CASE HISTORIES

Case 1

This 3½-year-old-boy was briefly described in a prior report (Wilson *et al.*, 1986). He was the product of a term uncomplicated gestation. Enlarged anterior and posterior fontanelles, open metopic suture and a widened sagittal suture were present at birth. He was admitted at age 7 weeks for evaluation of poor weight gain, hypotonia and hepatomegaly. Laboratory investigation revealed anaemia and elevation of the serum bilirubin, alkaline phosphatase, SGPT and ferritin. Percutaneous liver biopsy showed increased glycogen with fibrous septa and paucity of intrahepatic ducts. At age 9 months ophthalmological evaluation showed inconsistent fixation and following of light, vertical nystagmus, bilateral punctate cortical and nuclear sclerosis lens changes with no cataracts, and marked peripheral retinal pigmentary changes. Visual evoked response and electroretinogram showed no photopic or scotopic responses suggesting a poor outlook for vision.

Assays for DHAP-AT and plasmalogens performed at age 14 months were abnormal and he was started on oral ether lipid supplementation. After 3 months

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of treatment there was improved growth and muscle tone, decreased nystagmus and improved ability to follow light and fixate. Fundoscopic examination showed virtual disappearance of retinal pigmentation.

He has continued to improve and attends special education school. Visual acuity has not been measured but he can avoid obstructions while walking and walks towards and reaches for toys.

Case 2

This 4-year-old girl was delivered at term by caesarean section because of maternal eclampsia and weighed 2.7 kg. Routine neonatal screening of serum thyroxin was low and thyroid replacement therapy was begun. She was a poor feeder with poor weight gain and at age 6 months was admitted for evaluation of failure to thrive and developmental delay. Clinical findings included hepatomegaly, ascites and pericardial effusion. Total serum proteins were low and values of SGOT and SGPT were elevated. Percutaneous liver biopsy revealed periportal fibrosis and accumulation of glycogen. The ascites resolved and she was discharged.

At age $2\frac{1}{2}$ years she was re-evaluated because of developmental delay, failure to thrive, hypotonia, seizures and hepatomegaly. She was euthyroid, but assays for DHAP-AT activity and erythrocyte plasmalogens were abnormal. Oral ether lipid treatment was begun.

After 18 months of therapy her muscle tone and general state of awareness have improved. She is able to walk and is auditorially and visually alert. Sequential developmental and psychomotor evaluations in a special education programme have shown progress in social/emotional, cognitive, language and motor skills.

MATERIALS AND METHODS

Assays for DHAP-AT activity were performed as described by Datta and colleagues (1984). Plasmalogens were measured as previously described (Wilson *et al.*, 1986). Very long chain fatty acids in plasma were fractionated and quantitated by the method of Moser and colleagues (1984).

The ether lipid mixture contains 400 mg of batyl alcohol and 200 mg of sodium deoxycholate in 100 mL of water. Each patient has been receiving 5 mL of this suspension daily, equivalent to 20 mg batyl alcohol per day for the past year. Prior to that they had been receiving an ether lipid suspension containing batyl alcohol, chimyl alcohol and selachyl alcohol as previously described (Wilson *et al.*, 1986).

RESULTS

Fibroblast DHAP-AT activity in patient 1 was 0.14 nmol min^{-1} (mg protein)$^{-1}$ and 0.12 nmol min^{-1} (mg protein)$^{-1}$ in case 2. Each patient had approximately 50% of control activity.

Erythrocyte phosphoethanolamine plasmalogen composition in patient 1 at age 14 months just prior to starting treatment was 4% of total phospholipids (control

10%). Following treatment the levels have been: 7.9% (age 20 months), 9.8% (age 25 months), and 10% (age 33 months). The level in patient 2 prior to treatment was 1.3% (age 30 months), and following treatment has been 11.1% (age 34 months) and 11.2% (age 46 months).

Very long chain fatty acids were elevated in the plasma of patient 1 and were normal in patient 2. Repeat levels in patient 1 did not change during treatment.

DISCUSSION

Administration of oral ether lipids represents a potential treatment for patients with peroxisomal disorders and the multiple consequences of peroxisome deficiency. Although both of our patients are clinically improving and their erythrocyte phosphoethanolamine plasmalogen composition has returned to control levels, the efficacy of ether lipid therapy is not clear. Comprehensive therapy for patients with peroxisomal defects has not been determined, and severely affected patients may not be amenable to treatment.

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