Human Essential Fatty Acid Deficiency

Treatment by Topical Application of Linoleic Acid

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- An essential fatty acid (EFA) deficiency developed in a 19-year-old man who was being maintained on a long-term regimen of fat-free, intravenous hyperalimentation fluids. The EFA deficiency was reversed after 21 days by daily, topical application of linoleic acid to the patient's skin. The ratio of eicosatrienoic acid (20:3, n-9) to eicosatetraenoic acid (20:4, n-6) decreased to normal levels in the skin and serum with clinical improvement of the EFA deficiency syndrome. The cutaneous manifestations (scalp dermatitis, alopecia, and depigmentation of hair) were reversed with continued, topical application of safflower oil, which contains 60% to 70% linoleic acid. (Arch Dermatol 113:939-941, 1977)

Essential fatty acid (EFA) deficiency has been described in rats, mice, dogs, swine, and humans. The essentiality of a polyunsaturated acid is that the double bonds must have cisconfiguration as in linoleic acid and arachidonic acid. Arachidonic acid is three to five times as effective as linoleic acid in promoting growth. However, linoleic acid is the essential fatty acid that can be most easily obtained from the diet in preventing EFA deficiency.

Rats, dogs, mice, and pigs that were fed EFA-deficient diets developed eczema, dry, scaling skin, tail necrosis, renal edema, and sterility. Infants who were fed low-fat diets developed thrombocytopenia, dry, scaling skin, or dermatitis; they gained weight slowly, and their bodies had a poor ability to heal wounds. In addition to these clinical signs, EFA-deficient animals and humans have an abnormally high serum concentration of the fatty acid eicosatrienoic acid (20:3, n-9) and a low serum concentration of arachidonic acid (eicosatetraenoic acid, 20:4, n-6). The increased 20:3/20:4 ratio is diagnostic of EFA deficiency.

In a well-controlled study, Prottey and co-workers demonstrated in three cases that the cutaneous application of sunflower-seed oil (rich in linoleic acid), but not olive oil, reversed the effects of EFA deficiency caused by chronic malabsorption, and it increased the levels of epidermal linoleic acid.

With the increased use of long-term, parenteral nutrition, many patients may develop EFA deficiency. Supplementation of their diets with linoleic acid is, therefore, imperative. Since a previous study from our laboratory showed that topical prostaglandin E (PGE) cleared scaly skin lesions of EFA-deficient rats, we investigated the effect of topical applications of linoleic acid, which is an endogenous precursor of arachidononic acid, prostaglandin E (PGE), and PGE, on the skin of a patient who was being fed fat-free fluids by intravenous hyperalimentation.

METHODS

The patient was a 19-year-old man with severe, inflammatory bowel disease, who had had a colectomy following a sudden perforation of his transverse colon. After receiving fat-free fluids by intravenous hyperalimentation for four months postoperatively, he developed dermatitis of the scalp and eyebrow areas, a diffuse scalp and eyebrow alopecia, and a lightening of his remaining scalp hair (Fig 1). He still required intravenous hyperalimentation because of an abdominal wall defect and bowel-to-skin fistulas.

The intravenous hyperalimentation fluids contained the essential and nonessential amino acids, dextrose, and water, all in varying concentrations. Multivitamins that were added to the intravenous fluids included ascorbic acid, vitamin A, vitamin D (ergocalciferol), thiamine hydrochloride, riboflavin (as 5-phosphate), pyridoxine, niacinamide, dexamethosol, and vitamin E (di-alpha tocopherol acetate). The patient had been receiving these substances prior to and after development of the cutaneous manifestations of EFA deficiency.

Five milliliters of venous blood and one 4-mm skin punch biopsy specimen were taken from the left thigh at each of three different times and analyzed for the determination of fatty acids. The blood and skin specimens were obtained before treatment and at seven and 14 days after treatment. The patient was treated topically with 150
mg of linoleic acid, which was carefully rubbed into the skin of his right thigh once a day for 21 days. Topical treatment with safflower oil (containing approximately 60% to 70% linoleic acid) replaced the linoleic acid applications to the right thigh after three weeks.

Analysis of Fatty Acids

The skin biopsy specimens were homogenized rapidly in chloroform:methanol, 2:1 (v/v) and the total lipids were extracted according to the procedure described by Folch et al.' The same method was used to extract the lipids from the serum. The total lipids from serum and skin were transesterified by refluxing under nitrogen for two hours with a 5% solution of hydrochloric acid in methanol. The methyl esters of the fatty acids were analyzed by gas-liquid-chromatography with a hydrogen flame ionization detector. The methyl esters were identified by internal standards of reference methyl esters of fatty acids (purity 95% to 99%). Quantification of fatty acid peaks was by triangulation.

Effects of Ultraviolet Light (UV-B) on Skin

The patient's response to ultraviolet light (UVL) irradiation was tested before and after topical linoleic acid therapy. Two sun tubes (major emission 290 to 320 nm; intensity, 2,000 µW/cm² at 10 cm) were used to irradiate 1 × 2-cm rectangular areas of the patient's left, volar forearm for various times at 30-second intervals. The minimal erythema dose (MErD), which is defined as the minimum dose of UVL necessary to produce erythema 24 hours after irradiation, was determined.

RESULTS

After three weeks of topical therapy with linoleic acid, the scaling dermatitis of the patient's scalp resolved. Regrowth and repigmentation of his scalp and eyebrow hair occurred after three months of topical therapy (Fig 2). The topical safflower oil therapy was continued for the period during which the patient was maintained on intravenous hyperalimentation fluids, because his fistulous bowel disease prevented oral intake of solid foods and fluids.

The ratios of eicosatrienoic acid (20:3, n-9) to eicosatetraenoic acid (20:4, n-6) in the sera and skin specimens are shown in the Table. The ratio of the 20:3/20:4 fatty acids in the serum and the skin on admission into the hospital was increased greatly, demonstrating a clear case of EFA deficiency. After two weeks of topical treatment with linoleic acid, the ratio of these fatty acids was decreased to normal level in the skin. Although the ratio was still high in the serum, a notable drop had occurred from the pretreatment value. The MErD was the same and within normal range both before and after three months of linoleic acid therapy.

COMMENT

Our findings showed that a 19-year-old man who had been maintained on a long-term regimen of fat-free, intravenous hyperalimentation fluids developed signs of EFA deficiency. In addition to the cutaneous lesions, we found a marked increase in the ratio of 20:3/20:4 fatty acids in the patient's skin and serum. After three weeks of topical treatment with linoleic acid, the improvement of the dermatitis was parallel with a return to normal level of the 20:3/20:4 fatty acid ratio in the skin. A prominent decrease in this ratio also occurred in the serum (Table). These results indicate that linoleic acid was absorbed percutaneously and metabolized systemically to arachidonic acid (20:4, n-6). Percutaneous absorption of linoleic acid by EFA-deficient patients in whom correction of the cutaneous signs and the serum fatty acid ratio levels has taken place is well described.** Correction of the skin 20:3/20:4 fatty acid ratio at sites distant from the linoleic acid applications has not been previously reported. The mechanism of action of

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**Table:**

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<th>Day</th>
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<th>Skin</th>
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<tr>
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<td>1.6</td>
</tr>
<tr>
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</tr>
<tr>
<td>14</td>
<td>0.8</td>
<td>0.4</td>
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*Ratio of 20:3/20:4 > 0.4 denotes essential fatty acid deficiency syndrome.*

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Fig 1.—Patient before topical essential fatty acid supplementation.

Fig 2.—Patient after three months of topical therapy. Note regrowth and pigmentation of hair.
linoleic acid in reversing the skin signs of EFA deficiency is unknown. It is interesting, however, that Ziboh and Haśa reported the clearing of scaly lesions in the skin of EFA-deficient rats with topical PGE. Since linoleic acid is an endogenous precursor of PGE, the possibility that the prostaglandins or their intermediates are involved in the reversal of the cutaneous signs associated with EFA deficiency is likely and deserves further study.

Of particular interest in this study is the regimention and growth of new scalp and eyebrow hair by the patient after several months of daily topical treatment with safflower oil. An analogous “browning” of normally black hair has been reported in EFA-deficient hooded rats. These observations suggest that a relationship might exist between pigmentation, hair growth, linoleic acid, and its metabolites. Prostaglandins have been reported to disperse melanosomes in black goldfish and to darken frog skin. Further studies are necessary to elucidate possible relationships.

Since the E series prostaglandins are reported to be important mediators of UVL-induced redness, it is surprising that the patient’s MEmD was normal before correction of his EFA deficiency. While EFA-deficient, the patient had reduced EFA precursors of PGE and an elevated skin concentration of eicosatrienoic acid (20:3, n-9), which is an inhibitor of prostaglandin synthesis.

Our findings illustrate the need to supply linoleic acid to patients whose sole source of nutrition is fat-free fluids by intravenous hyperalimentation. Linoleic acid supplementation may also be necessary for patients suffering from fat malabsorption. Topical application of safflower oil is an effective and inexpensive method of dietary supplementation.

References