

Essential Fatty Acid Deficiency in Human Adults During Total Parenteral Nutrition

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Three patients undergoing prolonged total parenteral nutrition at home developed skin lesions, characterized by dryness and scaly appearance, initially confined to the folds but becoming subsequently generalized. Fatty acid measurements in plasma of these patients showed a markedly abnormal lipid pattern: accumulation of 5,8,11-eicosatrienoic acid (20:3 ω 9) and a high 20:3 ω 9-to-20:4 ω 6 ratio. When parenteral fat (Intralipid[®]) was administered, 500 ml/day, serial measurements of fatty acids showed a progressive normalization of the abnormal pattern and a dramatic improvement in the skin lesions. It appears that the daily requirement for linoleic acid in the adult, particularly during the period of rapid anabolism, has not been clearly established. Because more and more patients are becoming partly or totally dependent on parenteral nutrition for prolonged periods of time, the availability of parenteral fat preparations is urgently needed.

ESSENTIAL FATTY ACID DEFICIENCY has been delineated in experimental animals (1), and several case reports have described the condition in some infants on prolonged fat-free parenteral nutrition (2, 3). However, its occurrence in the human adult associated with skin lesions has not been encountered until recently (4). A curious set of circumstances now has resulted in the development of full-blown essential fatty acid deficiency in adults. The successful *long-term* parenteral nutrition in the home (5), together with the continued Federal Drug Administration ban on intravenous fat, set the stage for the development of this complication.

We report here three cases in which skin lesions occurred in association with a markedly abnormal plasma lipid pattern. Both abnormalities were corrected with intravenous fat emulsion.

Material and Methods

The subjects of this study are part of a group of 29 patients that have been maintained on parenteral nutrition in the home. All had been referred to the University Hospital because of severe malnutrition. Access to the circulation has been accomplished through a right atrial catheter as previously described (6). All received a standard solution that varied only in its

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electrolyte content. To a 2-litre bottle, which contains 1 litre of fluid and 600 g of glucose, the following is added: Freamine[®] II, 8.5% 10 dl (approximate concentration of amino acids [g/dl]: L-isoleucine, 0.59; L-leucine, 0.77; L-lysine HCl, 0.87; methionine, 0.45; L-phenylalanine, 0.48; L-threonine, 0.34; L-tryptophan, 0.13; L-valine, 0.56; L-alanine, 0.60; L-arginine, 0.31; L-histidine, 0.24; L-proline, 0.95; L-serine, 0.50; glycine, 1.7; L-cysteine HCl:H₂O < 0.02); NaCl, 90 to 120 meq/litre; KCl, 60 to 120 meq/litre; K₂PO₄, 20 to 60 meq/litre; calcium gluceptate, 4.5 to 9.0 meq/litre; MgSO₄, 16 to 32 meq/litre; Berocca-C[®], 2 ml alternating with Vi-Syneral[®], 2 ml. Each 2 ml of Berocca-C contains: thiamine hydrochloride, 10 mg; riboflavin, 10 mg; niacinamide, 80 mg; pyridoxine hydrochloride, 20 mg; panthenol, 20 mg; d-Biotin, 0.2 mg; ascorbic acid, 100 mg. Each 2 ml of Vi-Syneral provides Vitamin A, 10 000 USP U; Vitamin D, 1000 USP U; ascorbic acid, 50 mg; thiamine HCl, 10 mg; riboflavin, 1 mg; niacinamide, 20 mg; pyridoxine HCl, 3 mg; dexpanthenol, 5 mg; Vitamin E, 2 IU. Folic acid, 1 mg, and copper sulfate, 1 mg, also are added daily. Vitamin K and B-12 are given weekly and monthly, respectively. Maintenance therapy at home is usually accomplished with 10 056 kJ [2400 cal] per day infused at night during 12 to 14 h.

The following tests were obtained before therapy and at monthly intervals: complete blood cell count, serum electrolytes, blood urea nitrogen, creatinine, serum proteins, liver function tests, thyroid function tests, serum cholesterol and triglycerides, fatty acids, serum copper, and ceruloplasmine.

FATTY ACID ANALYSIS

One millilitre of plasma was extracted by the method of Folch, Lees, and Sloane-Stanley (7). The total lipid extract was taken to dryness and dissolved in 0.5 ml of freshly prepared 0.5 N KOH in methanol. The tube was flushed with nitrogen and the reaction allowed to proceed for 15 min at room temperature. The reaction was stopped by adding 0.05 ml of glacial acetic acid. After adding water, the fatty acid methyl esters were extracted into petroleum ether (bp, 30-60). The petroleum extract was washed several times with water and then dried over Na₂SO₄. The solvent was removed under vacuum and the residue dissolved in CS₂ for gas liquid chromatography. Gas liquid chromatography analysis was carried out using a Hewlett-Packard Model 402 (Hewlett-Packard Co., Palo Alto, California) with a flame detector and a Model 3370A integrator. A 1.8288-m × 0.4-cm (internal diameter) column of diethyleneglycol succinate (15% on Gas Chromosorb P, 100-120 mesh, Alltech Associates, Arlington Heights, Illinois) maintained at 190 °C (flash evaporator 200 °C; detector 265 °C; carrier gas, Helium 70 ml/min) was used. Fatty acid standards were obtained from the Hormal Institute (Austin, Minnesota). All analyses represent the average of two runs on each sample. The data presented represent only those fatty acids that showed significant changes. Minor amounts of other fatty acids (totalling less than 5%) also were present.

Case Reports

PATIENT 1

A 60-year-old white woman was admitted on 19 June 1974 with advanced malnutrition secondary to short bowel syndrome. Bladder carcinoma had been diagnosed in 1962 and initially treated with radiotherapy and later cystectomy. Repeated small bowel obstruction led to several intestinal resections that resulted in a short bowel (20 inches). No oral intake was allowed as part of management of an enterocutaneous fistula. Forty-six days after initiation of hyperalimentation her skin was noted to be dry and scaly, particularly on the axilla, elbows, and groin (Figure 1A). During this period her body weight increased from 29.0 kg to 36.0 kg. Intravenous fat providing 5.3% of total joules in the form of linoleic acid was administered daily (Intralipid®, 10%). Initially, the skin lesions became more generalized, resulting in exfoliative dermatitislike picture. After 14 days of daily intravenous fat therapy, her skin had cleared completely (Figure 1B).

PATIENT 2

A 53-year-old white woman was admitted in May 1973 because of malabsorption secondary to intractable sprue. Malabsorption had been present since 1966, and she had done reasonably well on a glutenfree diet. However, in the period before admission she experienced severe diarrhea and weight loss. After 6 months of total parenteral nutrition (oral intake practically negligible), her skin appeared dry, scaly, and erythematous. During this period she increased her body weight from 30.0 kg to 34.4 kg. The skin lesions were confined mainly to axilla, antecubital fossa, and around the neck and groin (Figure 2A). Five hundred millilitres of a 10% intravenous fat emulsion (Intralipid) was administered daily, providing 8% of total joules in the form of linoleic acid. Seven days later a marked improvement could be seen. Erythema and scaling had disappeared. Four weeks later her skin appeared smooth and shiny (Figure 2B).

PATIENT 3

A 13-year-old white girl with the diagnosis of systemic mast cell disease and chronic malabsorption was admitted on 21 June 1973 because of generalized dry skin and lichenification areas. She had been on total parenteral nutrition for approximately 2 years with essentially no oral intake. Her body weight increased from 19.0 kg to 30.0 kg. With the presumptive diagnosis of essential fatty acid deficiency, Intralipid 10% was administered daily, providing for the first 2 weeks 10% of the total joules in the form of linoleic acid. For the remaining period of treatment she received only 2% of the total joules in the form of linoleic acid. A week later her skin appeared less dry but still scaly. At the end of the sixth week only signs of urticaria pigmentosa were present.

Results

SKIN LESIONS AND THEIR RESPONSE TO PARENTERAL FAT

Three patients developed skin lesions. All were severely malnourished at the outset. The signs of severe exfoliative dermatitis became manifest after 46 days, 6 months, and 2 years, respectively, in these three cases, during which period all had received fatfree parenteral alimentation. In all, improvement was evident at the end of the first week of intravenous fat administration. In Patient 1, lesions were initially discrete, localized to body folds but becoming generalized within 3 days during fat infusion (Figure 1A). However, around the seventh day the skin, though still dry, was less flaky. At the end of the second week it appeared entirely normal (Figure 1B). In Patient 2, skin lesions were more impressive (Figure 2A). Erythema was marked, along with the dry and scaly appearance. With daily fat infusion all lesions had disappeared at the end of the second week (Figure 2B). In Patient 3, skin was hyperpigmented as part of the underlying mast cell disease. Although scaling was less prominent at the end of the second week, the skin was still dry and scaling was questionable around the eighth week of fat therapy.

PLASMA LEVELS OF FATTY ACIDS

Results of fatty acids determination before and during fat infusion are shown in Table 1. The most characteristic aspect of essential fatty acid deficiency is the accumulation of 5,8,11-eicosatrienoic acid (20:3_ω9), which is derived from 18:1_ω9 and is usually present only in trace amounts in normal subjects. Note the marked elevation of this fatty acid in all three cases (7.4%, 5.3%, and 6.6%). There is a concomitant decrease in 18:2_ω6, 20:4_ω6, and 20:3_ω6, which is derived from 18:2_ω6. Also to be noted are the elevated levels of palmitoleic (16:1) and oleic (18:1) acids. These latter fatty acids are presumed to increase due to accelerated synthesis (8). During fat infusion there was a progressive decrease in 20:3_ω9, and at the end of the third week this fatty acid was not detectable in Patient 1. There was a concomitant increase in 18:2_ω6, 20:4_ω6, and 20:3_ω6, and a decrease in the monounsaturated fatty acids (16:1 and 18:1). The ratio of 20:3_ω9 to 20:4_ω6 has been used to describe the severity of essential fatty acid deficiency (9). Normal values are below 0.4 (10). Before



Figure 1A. Patient 1. Appearance of the skin before fat therapy. B. Complete resolution within 2 weeks.

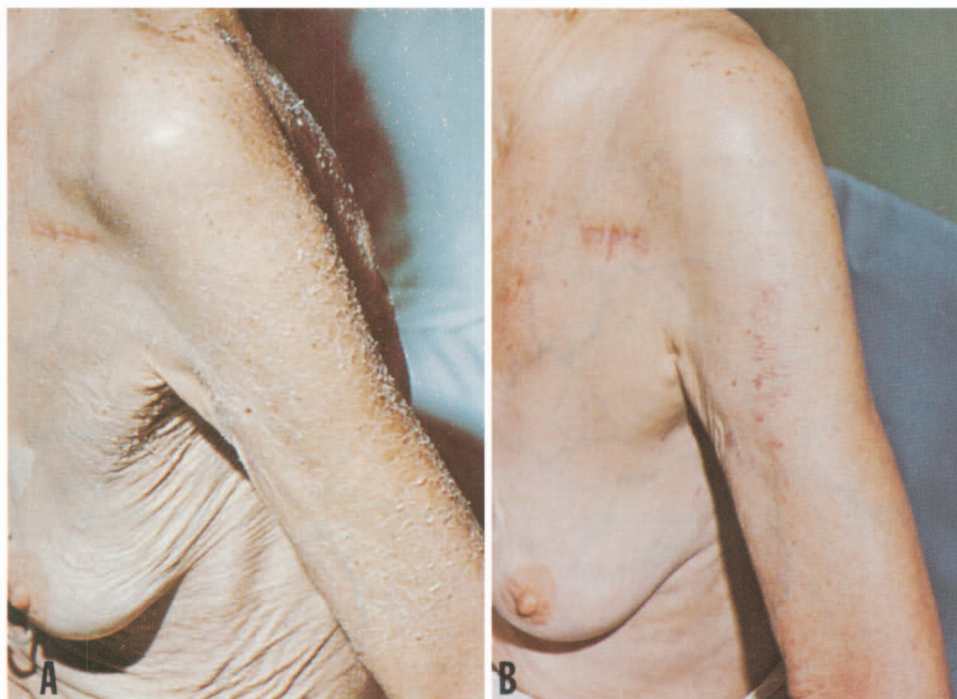


Figure 2A. Patient 2. Severe exfoliative dermatitis in patient before treatment. **B.** Two weeks after daily administration of 500 ml of Intralipid®.

fat infusion, this ratio was 3.7, 13.3 and 6.0 for Patients 1, 2, and 3, respectively. Within 1 week of fat infusion it had dropped to 0.3, 0.6, and 0.5 for Patients 1, 2, and 3, respectively.

Table 1. Percent of Total Plasma Fatty Acids Before and During Fat Administration*

Fatty Acids	Patient Number	Before Therapy	During Therapy			Normal Values (Mean ± SD)
			1st Week	3rd Week	4th Week	
16:0	1	28.3	35.3	31.9	32.7	30.9 ± 1.7
	2	31.6	31.9	31.2	32.7	
	3	31.7	27.1	...	29.9	
16:1	1	10.8	3.8	3.0	3.2	1.9 ± 0.9
	2	18.0	8.5	8.7	9.4	
	3	11.3	4.4	...	9.1	
18:0	1	8.1	16.8	17.8	15.6	12.9 ± 1.2
	2	3.7	7.2	6.2	7.2	
	3	6.6	12.5	...	9.8	
18:1	1	39.7	25.0	24.7	20.9	13.9 ± 1.9
	2	38.4	30.1	27.2	30.8	
	3	41.8	23.7	...	32.2	
18:2	1	3.8	12.2	14.3	17.3	21.5 ± 2.8
	2	2.6	13.9	21.6	12.9	
	3	0.9	21.7	...	7.4	
20:3 ω 9	1	7.3	1.4	N.D.	N.D.	N.D.
	2	5.3	2.6	0.9	0.7	
	3	6.6	2.8	...	3.2	
20:3 ω 6	1	N.D.	0.8	1.5	2.8	2.5 ± 1.2
	2	N.D.	1.7	1.1	2.0	
	3	N.D.	1.7	...	1.8	
20:4	1	2.0	4.7	6.8	7.5	7.1 ± 1.4
	2	0.4	4.1	3.0	4.3	
	3	1.1	6.0	...	6.6	
20:3 ω 9/ 20:4	1	3.7	0.3	0	0	<0.4
	2	13.3	0.6	0.3	0.2	
	3	6.0	0.5	...	0.5	

* N.D. = Not detected.

Discussion

It has become progressively more evident that fat preparations should be included in any program of long-term parenteral nutrition. Animal models have provided significant evidence of systemic changes in the course of essential fatty acid deficiency. Young rats made essential fatty acid deficient have a diminished growth rate, develop a scaly skin, roughened hair coat, and necrosis of the tail (1). Lipids are deposited in the liver (11), and kidney damage in these animals is described (12).

Adult rats on fatfree diets do not develop the classical signs of fat deficiency readily. However, it has been shown that if severely malnourished adult rats (reduced to half their starting weight) are given fatfree diets, they manifest classical fat deficiency symptoms along with the gain in weight (13). This sequence is similar to the situation in which the severely malnourished human adult using the artificial gut system is restored to normal nutrition without provision of parenteral fat (14). Rapid development of essential fatty acid deficiency was observed in our Patient 1 who was admitted in a state of advanced malnutrition. Her skin was noted to be dry and scaly 46 days after initiation of hyperalimentation.

In humans, the effect of a low-fat diet for an extended period of time was first investigated by von Gröer (15). Since then, several reports have dealt with clinical manifestations of essential fatty acid deficiency, namely dermatitis and recurrent infections in infants (16). The clinical expression of this deficiency is accompanied by a characteristic abnormal lipid pattern in the plasma (8, 17). Three cases here described exemplify this pattern. All had an accumulation of 5,8,11-eicosatrienoic acid which fell markedly upon administration of fat. The same enzyme system, which normally converts linoleic acid (which cannot be biosynthesized) to arachidonic acid, elongates and desatu-

rates oleic acid (18:1) when linoleic acid is reduced. The result is the production of 5,8,11-eicosatrienoic acid rather than arachidonic (18). Patient 3 who initially received 10.5% of total joules in the form of linoleic acid, had a rise in the content of 5,8,11-eicosatrienoic acid when the amount of linoleic acid administered per day was reduced to 2% of total joules. Minimum requirements of linoleic acid have been calculated as per cent of total joules. In infants, it has been estimated at 1% to 4% of total joules: that is, 25-100 mg/kg-day (19). However, Jeejeebhoy and associates (20) were unable to prevent the development of skin lesions in an adult with 50 g, and even 100 g of Intralipid per week. It seems that the parenteral fat requirement to prevent essential fatty acid deficiency, particularly during the phase of rapid anabolism, has not been clearly established.

Press, Hartop, and Prottey (21) have made an important contribution by showing that cutaneous application of sunflower seed oil to one forearm resulted in sufficient absorption to correct essential fatty acid deficiency, and, therefore, could serve as an alternative method of preventing it (21). However, intravenous fat has many other advantages. It is a concentrated source of energy (9 kg J/g), it can be administered into a peripheral vein thereby avoiding a central venous line, and it provides an alternate source of joules as it could at least in part replace glucose and permit shortening of the infusion time in the home (22).

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