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Increased Requirements for Essential Fatty Acids in Atopic Individuals: A Review With Clinical Descriptions

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Patients with atopic eczema and a mixture of allergic illnesses show biochemical evidence suggesting impairment in the desaturation of linoleic acid and linolenic acid by the enzyme delta-6 dehydrogenase. Consequences of this enzyme defect are 1) diminished synthesis of the 20-carbon polyunsaturated fatty acids, which are prostaglandin precursors and 2) a reduction in the concentration of double bonds in the cell membrane. A distortion in the production of prostaglandins and leukotrienes, which might result from this block, can account for the immunological defects of atopy and a variety of clinical symptoms experienced by atopic individuals. Dietary supplementation with essential fatty acids relieves the signs and symptoms of atopic eczema, may improve other types of allergic inflammation, and may also correct coexisting symptoms as diverse as excessive thirst and dysmenorrhea. Further research is suggested to test the hypothesis that some atopic states represent a condition of essential fatty acid dependency owing to defective desaturation of dietary fatty acids.

Key words: essential fatty acids, atopy

INTRODUCTION

Essential fatty acids (EFA) play two important roles in human physiology. Both derive from their incorporation into the phospholipids of cell membranes. By virtue of their high degree of unsaturation and, hence, low melting points, they decrease membrane viscosity [1] and affect several aspects of membrane function. The coupling of hormone receptors to target enzymes, such as adenylate cyclase, is influenced by membrane viscosity [2], as is the activity of some ATPases involved in ion transport [3]. The second key physiological role of EFAs requires their hydrolysis from cell membrane phospholipids and their conversion to prostaglandins (PGs) and

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leukotrienes (LTs). Ample evidence exists to indicate that EFA consumption has a significant effect on the production and the distribution of PGs and LTs [4].

Atopy is a state of immunologic hypersensitivity in which abnormal membrane receptor activity [5] and abnormal PG or LT synthesis [6] may play a pathogenic role. The metabolic disturbances in atopic individuals include impaired formation of cyclic AMP [7] and abnormal production of and reactivity to numerous chemical mediators [5,8–11]. The concept that EFAs are involved in the development of the atopic state preceded the discovery of PGs and the emergence of contemporary ideas about membrane structure and function. It came from Hansen's observation that the skin of EFA-deficient animals bears some resemblance to the dry, scaly skin of patients with atopic eczema. Hansen [12] determined that EFA levels in pooled plasma from eczematous children were lower than those of normal children. He advocated dietary EFA supplementation for treatment of childhood eczema. Results of clinical trials were variable [13–19], and dietary treatment of eczema was eclipsed by treatment with adrenal corticosteroids. Even today, with the art of clinical observation being undervalued in medical education, knowledgeable dermatologists know that allergic individuals often have dry skin and follicular keratoses, another manifestation of human EFA deficiency [20].

EFA METABOLISM IN ATOPIC ECZEMA

Brown and Hansen [21] had found a higher than normal ratio of linoleate to arachidonate in plasma of children with eczema, but their methodology was crude and the metabolism of EFAs was poorly understood at the time. The pioneering work of Holman and his colleagues [22] in the application of gas chromatography to the study of human fatty acid analysis enabled investigators in England and Canada to take a closer look at the involvement of EFAs in atopy by comparing the phospholipid fatty acid profiles in plasma of patients with eczema and a control population [23,24]. The patients showed a variable increase in linoleic acid (LA; 18:2 n6) and a marked decrease in the products of LA metabolism. Although Dr. Holman has described LA metabolism extensively in the preceding paper, I have included a summary in Figure 1a. LA is the major dietary EFA. To exert its biological effects it must be desaturated and elongated alternatively and repetitively. The end product of this sequence is docosapentaenoic acid (22:5 n6). Critical intermediates are dihomogamma linolenic acid (DGLA; 20:3 n6) and arachidonic acid (AA; 20:4 n6), precursors of PGs and LTs. The first step in this sequence is catalyzed by the magnesium-containing desaturase enzyme delta-6 dehydrogenase (D6DH). An elevation of LA and a decrease in concentration of all its metabolites suggest an impairment in the activity of this enzyme.

The n3 polyunsaturates appear to be affected in parallel. Their normal metabolism is reviewed in Figure 1b. Levels of n3s in plasma are small and variable, so that significant changes can be hard to discern. Nonetheless, compared to controls [24] eczema patients show an elevation of alpha-linoleic acid (LNA; 18:3 n3) and a decrease in its long-chain metabolites. One of these metabolites, eicosapentaenoic acid (EPA; 20:5 n3), is a precursor of the trienoic PGs. Small amounts of EPA may have significant effects on PG production in vivo [25]. EPA is a potent competitive inhibitor of AA for PG synthetase and for the lipoxygenase that initiates LT synthesis [26–28]. Whereas some tissues, such as liver [29] and brain [30], possess a full

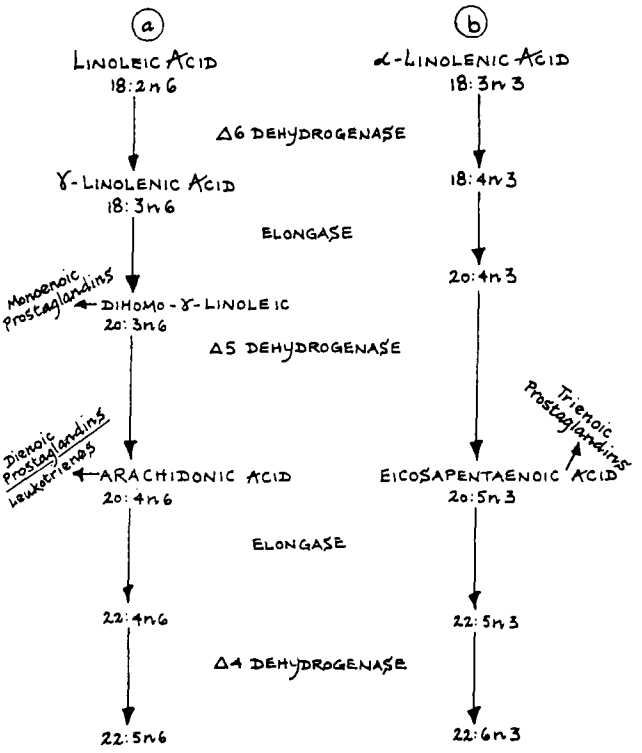

Fig. 1. Normal metabolism of EFAs.

complement of enzymes for PUFA synthesis, others, such as skin [31], granulocytes [32], and platelets [33], lack D6DH. They must extract 20-carbon EFAs for PG synthesis from plasma, an important transport step catalyzed by a specific arachidonoyl-CoA synthetase [33]. EPA is a potent inhibitor of AA transport into these cells. The n3 EFAs, therefore, exert multiple regulatory effects on n6 metabolism.

English investigators administered evening primrose oil (EPO) as a dietary supplement to patients whose EFA levels they studied [34]. Primrose oil was chosen because it contains 9% gamma linolenic acid (GLA; 18:3 n6), the product of delta-6 desaturation of LA. In a double-blind study using three levels of primrose oil (2.0, 4.0, and 6.0 gm daily) they found a significant, dose-dependent reduction in inflammation determined by pruritus, erythema, and scaling. EFA levels showed significant improvement as well [24]. This suggested that the intake of GLA was exerting not only a corrective effect on the usual skin signs of EFA deficiency, but an antiinflammatory and immunomodulatory effect. The investigators postulated that D6DH impairment in this group of atopic patients, with its resulting decrease in the levels of PG precursors, was impairing the synthesis of immunoregulatory prostaglandins [23].

STUDIES OF A HETEROGENEOUS GROUP OF ALLERGIC PATIENTS

Between January, 1983, and January, 1984, I studied the EFAs in plasma and erythrocyte phospholipids of a heterogeneous group of atopic patients presenting for

TABLE 1. Relative Percent Concentrations of EFAs in Plasma and Erythrocyte Phospholipids of Atopics and Controls

Fatty acid	Plasma			Erythrocytes		
	Atopy	Control	Normalcy index	Atopy	Control	Normalcy index
18:2 n6	25.43 ± 3.65	21.45 ± 2.81	1.18**	14.22 ± 2.14	9.78 ± 1.64	1.45**
18:3 n6	0.03 ± 0.06	0.16 ± 0.12	0.19**	—	—	
20:3 n6	2.54 ± 0.81	3.06 ± 0.60	0.83**	1.8 ± 0.42	1.37 ± 0.37	1.31**
20:4 n6	11.47 ± 2.54	11.36 ± 1.67	1.01**	17.81 ± 2.06	15.13 ± 1.98	1.18**
22:4 n6	0.46 ± 0.20	0.73 ± 0.26	0.63**	3.10 ± 0.78	5.54 ± 1.37	0.56**
22:5 n6	0.70 ± 0.18	1.12 ± 0.67	0.62**	0.78 ± 0.45	3.99 ± 1.85	0.20**
18:3 n3	0.17 ± 0.19	0.27 ± 0.53	0.62	—	—	
20:5 n3	0.63 ± 0.62	1.01 ± 0.36	0.62**	0.54 ± 0.53	0.65 ± 0.25	0.83
22:5 n3	0.70 ± 0.18	0.93 ± 0.27	0.75**	1.85 ± 0.38	2.53 ± 0.90	1.15**
22:6 n3	3.43 ± 1.24	3.54 ± 0.89	0.96	4.84 ± 1.27	4.20 ± 1.03	1.15*

*$P < 0.001$.
**$P < 0.0001$.

care to the Medical Department of The Gesell Institute. Diagnosis of atopy was based on the presence of symptoms consistent with atopic illness, such as chronic rhinitis, urticaria, asthma, eczema, a positive family history of allergy, and the presence of immediate hypersensitivity reactions to common inhalants as determined by intradermal testing. The fatty acids profiles were measured at Efamol Research Laboratory, Kentville, Nova Scotia, through the courtesy of Drs. David Horrobin and Mehar Manku, using a method previously described [23]. Patients ranged in age from 12 to 59 with a mean age of 28. There were 51 females and 22 males. The results are presented in Table 1, where they are compared with those of Efamol's standard reference population, which show plasma EFA values extremely close to the reference values established by Dr. Holman in Minnesota. The LA level in plasma is higher in the atopic patients, and the concentrations of almost all of its metabolites are significantly depressed; however, the AA concentration is normal. In the erythrocyte phospholipid fatty acids, the concentrations of LA, DGLA, and AA are all elevated compared to those of the control population, but the 22-carbon polyunsaturates are markedly depressed. The n3 fatty acids show no consistent pattern but tend to be lower in plasma and red cells in atopic patients than in controls. These results are not identical to those obtained in eczema; they suggest that diminished AA availability is *not* the critical link between EFAs and allergy.

Two aspects of the data were subjected to closer scrutiny: 1) the discrepancy between the concentration of AA and the concentrations of other LA metabolites and 2) the discrepancy between the plasma and erythrocyte EFA profiles. The distribution of plasma AA concentrations in the patient group follows a normal Gaussian curve and is inversely related to the LA concentration. Although it is possible that LA displaces AA from incorporation into plasma phospholipids, a large population study has shown a positive correlation between LA and AA levels [35]. The inverse correlation might, therefore, be a factor of the atopic state and might reflect the defect in LA desaturation described in atopic eczema [23,24]. Does a higher LA to AA ratio indicate a more severe block in EFA metabolism? To answer this question, I looked at 18 patients whose AA levels were more than 1 standard deviation above the mean

and compared them with 18 patients whose AA levels were more than 2 standard deviations below the mean. The only difference in the two groups was that a much higher percentage of the *high AA* patients showed dry skin than did the low AA patients (81% vs 50%), and there was a trend toward an inverse correlation between AA and the total concentration of n3 EFAs. Because the eczema patients with dry skin tended to show the most severe n3 EFA deficiencies (Horrobin, personal communication) and because the n3 EFAs compete with n6 EFAs for delta-6 and delta-5 desaturation [36], it is possible that a relative deficiency of n3 EFAs would allow increased formation of AA in some patients. Case studies, presented below, implicate an important role for n3 EFAs in human physiology.

Plasma phospholipids are synthesized in the liver [37]; their fatty acids reflect hepatic metabolism of dietary fats. Tissue phospholipids are more stable; they reflect intracellular metabolism *and* uptake from plasma. PGs are synthesized from a labile pool of membrane phospholipid fatty acids that are in flux with plasma phospholipids [38]. Total tissue phospholipid fatty acids are therefore less likely to reveal availability of EFAs for PG synthesis than are plasma phospholipid fatty acids. Red cell phospholipid fatty acids do reveal information on the status of structural membrane lipids. Manku et al [24] found a progressive impairment in atopics' metabolism of n6 EFAs at every step in the synthetic sequence. The data presented in Table 1 suggest that in atopic red cells the further elongation and desaturation of AA are very much impaired; this might account for the relative elevation of DGLA and AA. One consequence of this defect is likely to be an increase in cell membrane viscosity. The EFA double-bond index in red cell phospholipids, calculated by multiplying the number of double bonds in each fatty acid by its relative percent concentration, is 8% lower in the red cells of atopics than in controls ($P < 0.0001$).

The data obtained in this mixed group of 73 atopic individuals show their plasma and red cell phospholipid fatty acids to be distinctly different from controls. Red cell phospholipids have diminished concentrations of 22-carbon ultrapolyunsaturates. Plasma phospholipids have lower levels of DGLA and EPA, precursors of the monoenoic and trienoic PGs. These findings are consistent with impaired desaturation of dietary EFAs, as described in patients with eczema. The variability of AA levels in the mixed atopic population suggests the influence of other regulatory mechanisms, some of which might involve n3 EFAs.

PROSTAGLANDINS AND ALLERGY

A central event in the expression of allergic illness is the binding of immunoglobulin E (IgE) to mast cells with resultant releases of histamine (HA) and other inflammatory mediators. In addition to acting as an effector of allergic inflammation by stimulating H1 receptors, HA has immunosuppressive effects that are H2-mediated [39]. HA stimulates a population of suppressor T lymphocytes to produce a suppressor lymphokine called histamine-induced suppressor factor (HSF). The ability of lymphocytes to bind HA, and, therefore, to produce HSF, is a function of cell maturation [40]. HSF stimulates monocytes to produce E prostaglandins (PGE), which inhibit lymphocyte proliferation, lymphokine production, and antibody synthesis [41]. Atopic individuals show several immunologic deficiencies that can interfere with this carefully regulated negative feedback loop. Decrease in the number and function of suppressor/cytotoxic lymphocytes has been described by numerous investigators [42–

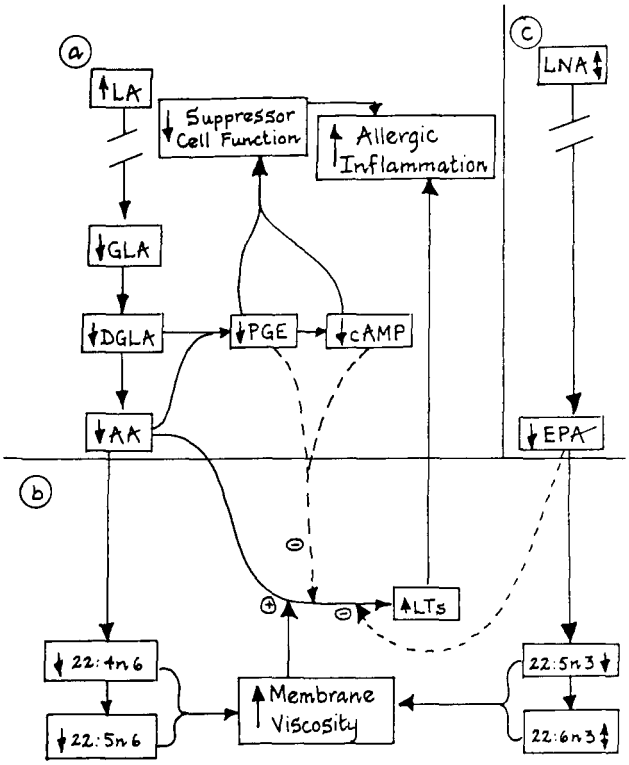

Fig. 2. The role of abnormal EFA metabolism in the genesis of atopy.

48]. Rocklin and his colleagues [49] demonstrated a decrease in lymphocytes bearing H2 receptors and, consequently, diminished formation of HSF by atopic lymphocytes. Suppressor T cells of atopics show abnormal responses to drugs that ordinarily increase intracellular cAMP [47]. Atopic monocytes produce less than 10% of the PGE2 in response to HSF that normal monocytes do; they require more HA to stimulate suppressor functions [48]. Atopic individuals, therefore, have higher circulating levels of HA [46,50]. These abnormalities are specific to atopy and not merely secondary to down-regulation of H2 receptors by high HA exposure [49]. They might all be explained by diminished PGE production. PGE1, a derivative of DGLA, encourages the maturation of T lymphocytes [51] and might enhance cytotoxic T-cell activity in vivo [52]. PGE1 and its analogue, PGE2 (derived from AA), maintain intracellular cAMP concentrations [53] and modulate the activation of adenylate cyclase by hormones [54] and neurotransmitters [55]. In higher physiological concentrations (10^{-6}–10^{-5} M) PGE1 inhibits HA release [56]. Decreased PGE1 production might explain the impaired T-cell maturation and cytolytic activity of atopics. T-cell immaturity would decrease H2-receptor development [40]. Impaired synthesis of PGE2 by monocytes might further attenuate the HA-induced negative feedback loop. Lack of PGE-stimulated adenylate cyclase activity might explain the altered response of atopic tissues to drugs and chemical regulators that express their effects through adenylate cyclase. A role for impaired LA desaturation in the immunology of atopy is illustrated in Figure 2a.

Excessive, rather than diminished, generation of PGs and LTs contributes to the appearance of many allergic symptoms, such as wheezing, mucorrhea, and edema [8]. LTs also play a critical role in HA release [57]. The first step in PG/LT synthesis is the hydrolysis of DGLA or AA from the cell membrane by the activity of a phospholipase. These enzymes are activated by calcium and inhibited by cyclic AMP [58]. PGE1, a potent stimulator of adenylate cyclase, inhibits phospholipase activity in human platelets [59]. Impairment of PGE production may allow increased phospholipase activity and increased synthesis of proinflammatory PGs and LTs. Analogous situations exist in cystic fibrosis [60] and Crohn disease [61], in which increased PG production accompanies decreased EFA levels. In fact, administering LA to patients with cystic fibrosis results in a decrease in the formation of $PGF2_{\alpha}$ [60]. Thus impaired EFA metabolism in allergic individuals would produce a distortion of PG/LT synthesis rather than a global decrease. Moreover, an increase in membrane viscosity might operate to activate phospholipase or impair adenylate cyclase. This concept is represented in Figure 2b.

The enzymes that metabolize LA also desaturate and elongate LNA [36]. While the enzymes of PUFA synthesis generally show a higher affinity for n3 EFAs, the n3 EFAs form a tiny fraction of total fatty acids, and dietary intake of n3 EFAs in industrialized countries has been declining over the past several decades owing to changes in food choices and the partial hydrogenation of vegetable oils [62]. The competitive relationship between n3 and n6 EFAs makes it likely that disturbances in n3 intake or metabolism can lead to altered PG synthesis. This effect is shown in Figure 2c. In that PGs regulate numerous cell functions in addition to immune modulation, disordered PG synthesis would be expected to produce diverse clinical manifestations. Our experience, described below in the case presentations, has been that a variety of nonallergic conditions occurring in atopic individuals will respond to dietary EFA supplementation.

CASE REPORTS

Over the past 2 years I have treated several hundred allergic individuals with EFA supplementation. Presented are a few cases that illustrate the diversity of responses and that meet the following criteria: 1) circulating EFA levels were measured prior to the initiation of treatment; 2) EFAs were introduced at some point in the therapeutic process as monotherapy; and 3) a clear-cut reversible response to EFA supplementation was discerned.

Although these patients did not present primarily for treatment of common allergic complaints, each has a strongly positive family history of atopic illness, chronic allergic symptoms such as nasal congestion, physical signs suggestive of allergy, and positive skin test reactivity to several common antigens. In patients 2, 5, and 6 plasma and erythrocyte phospholipid fatty acids were analyzed at Efamol Research Laboratory. In patients 1, 3, and 4 serum phospholipid fatty acids were measured at Monroe Medical Research Laboratory, Southfield, New York, using an adaptation of the method of Holman [22]. For each patient, the results of fatty acid analysis are presented in Table 2 using Holman's format of the normalcy ratio, which compares the measured relative percent concentration of each fatty acid with the expected relative percent concentration of that fatty acid based on studies of a control

TABLE 2. Phospholipid EFA Levels in Six Atopic Patients*

			n6 Series				n3 Series			
Case	18:2	18:3	20:3	20:4	22:4	22:5	18:3	20:5	22:5	22:6
1 S	1.35	0.06	0.46	0.61	—	—	0.12	0.21	—	0.07
2 P	1.15	—	0.54	0.74	0.47	0.14	2.82	0.55	.53	0.75
R	1.60	—	1.68	1.07	0.61	0.18	—	0.72	.74	1.30
3 S	1.74	2.78	0.90	3.55	—	—	0.23	0.22	—	0.39
S[a]	1.23	2.92	1.49	1.11	—	—	3.36	1.56	—	1.92
4 S	2.69	1.08	3.94	2.54	—	—	0.31	0.60	—	1.27
5 P	1.09	0.88	1.20	1.13	1.48	0.59	0.76	0.20	.71	0.97
R	1.52	—	1.51	1.18	0.53	0.19	—	0.84	0.68	1.18
6 P	1.11	—	0.63	1.21	0.45	0.29	1.69	1.31	.87	1.97

*Values expressed as normalcy index (see test for description). Case reports are in text. S, serum levels; P, plasma levels; R, red cell levels.
[a]Posttreatment values.

population. Calculation of the normalcy ratio utilized the reference values determined by the laboratory performing the measurements.

Case 1

A 6-year-old boy was brought in by his parents for evaluation of allergic and behavioral problems. He suffered from chronic nasal congestion and occasional cough and wheezing, developed hives if licked by a dog, and had episodes of irritability and crying, which his mother believed were produced by consumption of sweets. Also of interest was a history of apparently excessive thirst since infancy. The child study center of a major university had diagnosed attention deficit disorder, visual motor incoordination, and developmental immaturity and recommended treatment with Ritalin. Physical examination revealed a cooperative and pleasant youngster with dry skin, lackluster hair, numerous follicular keratoses, puffy eyes, a pale boggy nasal mucosa, and white spots on the fingernails. Routine laboratory tests showed hypereosinophilia and low serum ferritin. The EFA analysis is presented in Table 1. He showed an elevation of LA in serum phospholipids and depressed levels of the PG precursors, as has been described in eczematous patients and in hyperactive children [63]. In addition, the concentrations of all the n3 EFAs were low. He was placed on evening primrose oil (EPO), 2 gm daily, with a prompt reduction in thirst. Approximately 1 week later, his teacher noticed an increase in irritability and his mother a loss of appetite. The daily dose of EPO was reduced to 1 gm and then to 500 mg. On this last dose, his decreased thirst was sustained. At the end of 1 month, his mother reported that he no longer developed hives when licked by his neighbor's dog; he had less nocturnal congestion, his skin and hair were less dry, and he appeared calmer. An iron supplement and a salmon-oil extract (Max-EPA, 1 gm daily) were added to EPO. He was also started on a program of immunotherapy for allergy. Over the subsequent 9 months, his hair and skin became lustrous, the puffiness disappeared from his eyes, and he had no congestion or behavioral problems, even when challenged with sugar. After 9 months of treatment, EPO was temporarily discontinued during investigation of a retinal nevus. After 2 weeks, his parents noted an increase in thirst, the reappearance of sniffles, and a return of irritability and of hives in response to contact with dogs. Cough and wheezing developed, and bronchodilators

were required. After 1 month of this relapse, he restarted EPO 1 gm daily, and within a period of 10–14 days experienced normalization of thirst, clearing of nasal congestion, disappearance of hives, and improvement in mood and behavior. Asthma did not return. He has continued to do well over the last 19 months.

Comment

This case illustrates many of the characteristics we find to be common in allergic children who respond well to EFA supplementation. Excessive thirst is common; it has been noted in EFA-deficient animals [64] and in a population of allergic hyperactive children [65]. The mechanism of excessive thirst in experimental EFA deficiency is thought to be an increase in transdermal water loss owing to defective barrier function of the skin. It responds rapidly to treatment with LA or GLA but not with DGLA or AA [64]. How LA or GLA enhance dermal barrier function is uncertain. Although this child was treated with several interventions, all his symptoms returned and remitted with changes in his use of EPO. An excessive dose of EPO appeared to cause adverse side effects, in this case irritability and anorexia. Reversible toxic reactions to EPO overdosage are not unusual in allergic children; they confirm the physiologic potency of dietary GLA.

Case 2

This 26-year-old woman, with chronic fatigue and nasal congestion, presented for evaluation of dysmenorrhea of 7 years' duration. Physical examination disclosed dark circles under the eyes and a pale edematous nasal mucosa. Abdominal, pelvic, and rectal examinations were normal. Because dysmenorrhea is associated with increased production of $PGF_{2\alpha}$ from AA [66], supplementation was started with 15 gm/day of linseed oil (LSO), which contains 50% LNA. During the first month of therapy she experienced a 90% reduction in pain. After 3 months she became nauseated by LSO and was unable to swallow it. With discontinuation of LSO, her pain returned. EPO was ineffective in preventing pain but did not exacerbate it. Max-EPA, 3 gm daily, was tolerated by the patient but was not as effective as LSO. After 4 months of experimentation with various fatty acid supplements, the patient returned to the use of 15 gm LSO per day and improved her tolerance by mixing it with food. She again experienced marked reduction in pelvic pain.

Comment

The plasma phospholipids of this patient, reflecting hepatic EFA metabolism, reveal a block in D6DH activity affecting both n6 and n3 EFA families. The consequences of this block are the opposite of those in Case 1. Impaired LA desaturation produced no symptomatic clinical effect. Impaired LNA desaturation was apparently associated with pain, probably PG-mediated, that responded to LNA administration. This suggests that one physiological role of n3 fatty acids is the regulation of n6 metabolism and PG synthesis. A superior response to LSO compared to Max-EPA in this case is unexpected and might reflect the higher dose of LSO employed.

Case 3

A 55-year-old man presented for evaluation of chest pain. Three years prior to this evaluation, during a routine physical examination, he had been found to have

numerous multifocal premature ventricular contractions. Cardiac evaluation led to coronary angiography, which revealed a 99% stenosis of the left anterior descending coronary artery. Calcific aortic stenosis and mitral valve prolapse were also found. He had no chest pain at that time. After coronary artery bypass surgery he remained asymptomatic for 2 years and then began to experience fatigue and chest pain. The pain occurred daily, lasted for several hours, and was not exacerbated or precipitated by exertion. A thallium stress test and MUGA scan were normal. Repeat angiography showed the graft to be patent. The pain showed no response to therapy with a β-blocker and very limited response to treatment with a calcium channel blocker. He had a history of mild atopic dermatitis and complained of excessive thirst, dry skin, morning cough, and chronic rhinitis. On physical examination he had dry, strawlike hair, very dry skin with scaling and flaking of his hands, a midsystolic cardiac click with a late systolic murmur, and numerous white spots on his fingernails. Laboratory studies showed low red blood cell magnesium. EFA levels in serum showed an unusual pattern with very marked elevation of AA and slight depression of DGLA. All the n3 EFAs were markedly depressed. Therapy was initiated with magnesium and EPO, 3 gm daily. He was also placed on a low-fat diet. Within 2 weeks he experienced complete cessation of chest pain. When the results of the fatty acid profile were returned, he was started on Max-EPA, 3 gm daily. After 3 months of being pain-free, he developed a return of chest pain despite adherence to his diet and the nutritional supplements. Questioning revealed that 2 weeks earlier he had begun using a cheaper brand of EPO purchased from a mail order house. Subsequent analysis of that alleged EPO showed a negligible GLA content. When he resumed supplementation with 9% GLA primrose oil, his chest pain again disappeared. He remained free of pain for the next 11 months, until he again discontinued EPO. During the time of supplemented EFA intake, the dryness of his skin and hair improved dramatically and no scaling of his hands was evident. He also described improvement in thirst and energy. After 6 months of EFA therapy, the serum phospholipid fatty acid profile was again measured and revealed several significant changes. The concentration of AA had fallen to normal and the concentration of DGLA had increased by 50%. All the n3 EFAs were now present in excess.

Comment

The nature of this patient's chest pain is obscure. Atypical chest pain has been described in patients with mitral valve prolapse, but there is little agreement about its mechanism. If his serum phospholipid fatty acids are an indicator of his hepatic EFA metabolism, then he appears to have an overactivity of the delta-5 dehydrogenase (D5DH) and impaired activity of the elongase. One can speculate that consuming GLA and inhibiting D5DH with EPA raised the concentration of DGLA and lowered that of AA. An increased ratio of DLGA to AA in phospholipids would encourage the formation of PGE1, which, as a coronary vasodilator [67], would have a beneficial effect in variant angina. His excessive thirst and dry skin were present despite high levels of circulating n6 EFAs. They improved only when additional EPA was consumed. The role of EPA might have been to correct an n3 deficiency or to modify n6 metabolism by inhibition of D5DH.

Case 4

A 10-year-old boy was brought in by his mother for evaluation of enuresis and behavioral problems. He had always been quick tempered, restless, and socially

immature. A psychologist observed that he was afraid of his father and felt rejected by his parents. His pediatrician had diagnosed attention deficit disorder. His mother had placed him on the Feingold diet and reported that he was calmer; the pediatrician prescribed Ritalin, which also had a calming effect. Neither treatment affected his enuresis or encopresis, which had developed at the age of 8. Enuresis was occurring nightly and encopresis once or twice per week. He had a history of eczema and excessive thirst. Physical examination revealed dry, strawlike hair and somewhat dry skin. The serum fatty acid profile showed high levels of all measured n6 EFAs and low levels of the major n3 EFAs with no apparent block in EFA metabolism. Before the results of phospholipid analysis were available, the patient was arbitrarily started on linseed oil, 30 gm daily. Within 3 days he experienced a marked decrease in thirst and total cessation of enuresis and encopresis. There were no changes in social behavior. Substitution of EPO for LSO was associated with a rapid return of thirst, encopresis, and enuresis and with several episodes of uncommonly violent behavior. When LSO was restarted the enuresis, encopresis, and thirst again disappeared. Addition of Max-EPA to LSO had no further effect, and his social behavior remained abysmal.

Comment

I have since seen two other hyperactive boys who responded adversely during n6 supplementation and achieved variable degrees of benefit, including decrease in thirst, while taking LSO. Their fatty acid profiles were not measured. LNA exacerbates the water loss through EFA-deficient rat skin [64]. The rat model of EFA deficiency cannot, therefore, explain the response of these children to LSO. Nor is a "pharmacologic" effect of LSO in inhibiting PG/LT synthesis a likely explanation; PG-synthetase inhibitors such as aspirin do not relieve thirst or enuresis. In that the n3 fatty acids are important in nervous system structure and function, the response of this patient suggests an effect of LSO on the central nervous system.

Case 5

An 8-year-old girl presented for treatment of allergies. For most of her life she had experienced chronic rhinitis, cough, "sinus problems," stomach aches, frequent colds, and mild eczema. She slept poorly and was felt by her parents to be moody. On physical examination she had atopic dermatitis involving the right antecubital fossa, slight pulmonary wheeze, and a short systolic ejection murmur. The skin on her legs was dry and scaly and she had marked phrynoderma (follicular keratoses) of her thighs and arms. Treatment with EPO and immunotherapy for allergy produced no change in her skin, although her respiratory problems improved. LSO, 15 gm per day, increased skin oiliness, cleared her phrynoderma, and diminished the intensity of eczema. During the time of LSO therapy, she also noted an increase in energy and a decrease in congestion, but these might have been related to the immunotherapy that had started some months earlier. Replacement of LSO with Max-EPA, 2 gm daily, maintained the improvement in her skin.

Comment

In view of the finding that follicular keratoses are associated with EFA deficiency in malnourished children [20], it is likely that the response of this otherwise well nourished child to n3 supplementation represents a greater than normal requirement for these fatty acids for normal health of her skin. Her plasma phospholipids

show no specific pattern, but the EPA level is unusually low and might reflect a select effect of D6DH impairment on n3 metabolism.

Case 6

This 27-year-old woman professional athlete presented with a complex chronic illness of 2 year's duration characterized by fatigue, intermittent fever, chest pain, headaches, dysmenorrhea, and premenstrual mastodynia. All symptoms began after hospitalization for an acute, severe vulvovaginitis associated with high fever. The etiology of the original infection had not been determined, but its description suggested herpes simplex. During the 2 years prior to her evaluation at the Gesell Institute, she had consulted numerous medical specialists and was found to have prolapse of the mitral valve and many inhalant allergies. Resolution of her symptoms required several interventions and immunotherapy for allergy. I will discuss only the EFA therapy.

Because of the reported response of premenstrual mastodynia to EPO, pyridoxine, and magnesium [68], the patient was started on 3 gm per day of EPO, 100 mg per day of pyridoxine, and 300 mg per day of magnesium as the oxide. During the first month of treatment, there was slight improvement in mastodynia and dysmenorrhea. During the second month, she experienced a major exacerbation of both symptoms and in addition noted the development of increased perimenstrual pigmentation of her upper lip. I suspected that EPO in this patient was increasing the formation of PGs derived from AA, since $PGF2_{\alpha}$ is a major mediator of dysmenorrhea and PGE2 is a positive feedback modulator of estrogen formation in the ovary. Blood for plasma phospholipid fatty acids was drawn at this time. The patient was placed on a low-fat diet. EPO was discontinued and supplementation with LSO, 15 gm daily, and Max-EPA, 3 gm daily, was begun. Within 2 months there was complete disappearance of premenstrual mastodynia and dysmenorrhea. The perimenstrual melasma had also cleared. The patient began to complain of dry skin. The dose of Max-EPA was reduced to 2 gm daily, and EPO was reintroduced into the therapeutic regimen at a dose of 2 gm per day. Skin dryness cleared and there was no return of dysmenorrhea, mastodynia, or melasma. After several months of this therapy, the patient developed dryness and a loss of luster and body to her hair, which improved when Max-EPA was discontinued. After 29 months, she continues to find that supplementation with LSO, 15 gm every other day, is required to prevent dysmenorrhea.

Comment

This patient's EFA problems are much more complex than those of Case 2. Her plasma phospholipid fatty acid levels, drawn after 1 month of EPO, suggest a partially compensated block of D6DH (AA is normal; all other LA metabolites are low). Administration of n3 EFAs appeared to have made this block symptomatic, producing dry skin, which responded to EPO. The surprise is that levels of all her n3 EFAs were uncommonly high *before* n3 supplementation, and there is no evidence that n3 metabolism is blocked. One can speculate that tissue uptake of n3 EFAs is impaired in this patient, producing the high levels of circulating n3s and the clinical response to n3 supplementation. This untreated n3 dependency allowed exacerbation of her symptoms in response to n6 EFAs; its treatment permitted her to take n6 supplements without toxicity.

General Comments

These cases suggest that in some individuals dietary supplementation with relatively small doses of EFAs can produce striking clinical responses. Pronounced physiologic or pharmacologic effects of dietary EFA supplementation have been demonstrated in controlled studies of LA supplementation in diabetic angiopathy [69] and hypertension [70]; clinically significant immunosuppression has been obtained from 3 gm per day of EPO [71], and marked changes in platelet function have appeared after prolonged ingestion of small doses of LNA [72]. It is therefore possible that the clinical effects in these case reports are owing to pharmacologic actions of EFAs. The line between nutrition and pharmacology is quite hazy, however, and in each case the pretreatment analysis of phospholipid EFAs suggested an abnormality in EFA intake or metabolism. It is possible that these varied abnormalities in EFA levels derive from the impairment in D6DH activity that has been described in atopic eczema and that might be a common feature of atopics. The relative affinity of PUFA-synthetic enzymes for n3 EFAs, the level of n3s in the diet, and genetic or acquired variations in EFA transport modify the biochemical and physiological manifestations of the D6DH block.

The preliminary data presented in this report argue for further studies of EFA metabolism in varied groups of atopic patients. Controlled trials of EFA therapy should consider the following propositions: 1) EFA supplementation might alter numerous symptoms and signs, not only those under study. 2) EFA supplementation might have a long-term immunomodulatory effect. 3) The relative consumption of n3 and n6 EFAs might be as important as the absolute level of consumption; some individuals show a therapeutic response to n6 supplements and others show a similar response to n3 supplements.

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