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Successful Nutritional Intervention for an Infant with Abetalipoproteinemia: A Novel Modular Formula (AbetaMF)

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INTRODUCTION

Medical nutrition therapy is the only therapeutic alternative for several rare lipoprotein disorders. Abetalipoproteinemia (ABL; OMIM 200100), "homozygous" hypobetalipoproteinemia (OMIM 615558), and chylomicron retention disease (OMIM 246700), due to biallelic mutations in microsomal triglyceride transfer protein (*MTTP*), apolipoprotein B (*APOB*), and secretion-associated RAS-related GTPase 1B (*SAR1B*), respectively, are such disorders. Patients have extremely low total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and undetectable apolipoprotein B (apoB), due to defective biogenesis and secretion of apoB-containing chylomicrons from the intestine and very low-density lipoproteins from the liver (1). These lipoproteins normally carry cholesterol and TG as well as fat-soluble vitamins (2,3).

Clinical features of ABL and related disorders (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/PG9/A18), include fat-malabsorption associated with diarrhea or steatorrhea, resulting in failure to thrive. TG accumulation in enterocytes is visualized as "gelee blanche" endoscopically, and Oil Red O staining histopathologically (4). Ultrasound of the liver may reveal steatosis. Acanthocytes, spiculated erythrocytes due to altered membrane lipids, can be identified.

Other clinical manifestations (Table 1) result from deficiencies of essential fatty acids (EFA) and fat-soluble vitamins (9). Inadequate EFA intake retards growth and development (10). Vitamin E deficiency can lead to neurological manifestations including cerebellar dysfunction and impaired mobility (11). Ophthalmological abnormalities, primarily due to vitamin A deficiency, include night blindness, and atypical retinitis pigmentosa that can lead to blindness. Severe vitamin D deficiency can manifest in osteopenia or osteoporosis. Profound vitamin K deficiency can even cause hemorrhage (12).

CASE REPORT

A patient and her parent provided their consent for this report. The patient was born at full-term, birth weight 7 pounds (3.17 kg), and length 19.3 inches (48.9 cm). She was breast fed, but started refusing the breast at 2 weeks, associated with loose stools and vomiting. Multiple commercial formulas were tried without success by nasogastric tube, then by bottle. On Alimentum (Abbott, Columbus, OH), she lost 4 ounces, having 2 to 3 watery and curdy stools daily. On Neocate Infant (Nutricia, Gaithersburg, MD), she had no diarrhea, but stopped feeding.

Intestinal biopsy at 5 months for continued diarrhea revealed enterocyte vacuolization and abnormal villi. Acanthocytes and fat-soluble vitamin deficiencies were identified. Her lipid profile revealed TC <50 mg/dL, HDL-C 12 mg/dL, LDL-C <5 mg/dL, and undetectable TG. These findings, consistent with a clinical diagnosis of ABL or related condition, prompted fat-soluble vitamin supplementation (Table 2). ABL was confirmed via next-generation sequencing by identification of, maternal intronic (Int 13+5G>A – E13 skip) and paternal truncating (c.419_420insA, p.N140Kfs*1), known *MTTP* mutations.

At 6 months, because of continued feeding problems, the parents consulted a metabolic nutritionist who decided to prepare a nutritionally balanced modular formula for abetalipoproteinemia, we now refer to as AbetaMF. On AbetaMF, the patient had marked catch-up growth, and at 8 months, both height and weight increased from the <10th %ile to nearly the 50th %ile (Fig. 1A).

Her preference of AbetaMF persisted, and at age 2, only 5% to 10% of her diet was solid foods. She continued to consume some AbetaMF until almost age 5. She achieved all developmental milestones, sitting at 7 months and walking at 11-1/2 months. Growth and development continued to be age appropriate (Fig. 1B). She has had no neurological or ophthalmological abnormalities and no ultrasound evidence of hepatic steatosis. She is currently 17 years old and active in various sports. Her diet remains very low in total fat, yet nutritionally balanced.

A multivitamin (MVI) with marine omega-3 fatty acids had been added, and her fat-soluble vitamin dosages have been adjusted periodically while monitoring laboratory values.

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TABLE 1. Clinical features of abetalipoproteinemia due to deficiency of essential fatty acids and fat-soluble vitamins

	Biological importance	Clinical manifestation of deficiency
Essential fatty acids (5)	• Important in growth and development • Specifically, important in energy production, cell membrane synthesis, intracellular signaling molecules, and hormone production	• Growth retardation • Susceptibility to infection • Poor wound healing • Thrombocytopenia • Desquamating skin lesions
Docosahexaenoic acid (6)	• Important in visual and nervous systems • Critically important for retinal development, function, and regeneration of the visual pigment rhodopsin	• Learning disabilities • Poor visual and neural development
Arachidonic acid (7)	• Not one of essential fatty acids • Important in early neurological development, abundant in the brain	• May contribute to neuropsychiatric disorders
Fat-soluble vitamins (8)		
Vitamin A	• Important for formation and maintenance of skin, hair and mucous membranes • Plays a role in immune and reproductive systems • Important for component of rhodopsin	• Night blindness, dyschromatopsia • Atypical retinitis pigmentosa, blindness • Dryness and keratinization of the skin • Impaired immunity and hematopoiesis
Vitamin D	• Important in proper bone formation and calcium and phosphorus utilization in the body	• Rickets with severe deficiency • Periosteal bone pain • Osteopenia or osteoporosis
Vitamin E	• Lipid-soluble antioxidant that protects cells from free radical damages • Important in immune system	• Hyporeflexia, decreased proprioception, and vibratory sense • Cerebellar dysfunction (dysmetria, ataxia, and impaired mobility)
Vitamin K	• Important in the proper coagulation processes • Manufactured by bacteria normally found in the intestine	• Easy bruising • Coagulopathy • Hemorrhage with severe deficiency

TABLE 2. Recommended dosages of fat-soluble vitamin supplementation for abetalipoproteinemia and related disorders

	Recommended formulation	Recommended dosage (13)	Symptoms of vitamin toxicity*
Vitamin A	Water-miscible, PO	100–400 IU/kg/day	Skin irritation, bone abnormalities, headache, nausea, vomiting, rarely Pseudotumor cerebri syndrome
Vitamin D	D3 (cholecalciferol), Co-supplementation with D-alpha-tocopheryl polyethylene glycol succinate, PO	800–1200 IU/kg/day	Hypercalcemia, nephrolithiasis, weakness
Vitamin E	Natural (not synthetic) vitamin E mixture, PO (four isoforms of tocopherol)	100–300 IU/kg/day	No known toxicity reported
Vitamin K	Vitamin K1 (phytonadione), PO SC preferred for severe deficiency	5–35 mg/week	Flushing and peculiar sensations, and IV and IM form supplementations may trigger hypersensitivity and cardiac arrest
Notable vitamin Interactions (9,14)	• Vitamin E at moderate to high concentrations and vitamin A at high concentrations can reduce vitamin D uptake • Vitamin E uptake can be reduced by high vitamin A and D uptake • Vitamin E can interfere with vitamin K uptake		

*Only well-known examples are listed.
IM = intramuscular; IV = intravenous; PO = per os (by mouth); SC = subcutaneous.

Retinyl palmitate (vitamin A) at doses between 2,500 to 10,000 IU daily had been successful in keeping her retinol levels in the mid-normal range during infancy and childhood. Currently, 10,000 IU per day keeps the level in the low-normal range. The daily dosage of mixed natural tocopherols (vitamin E) has averaged 200 IU/kg. As often is the case in ABL, plasma α-tocopherol levels have never reached normal levels. Daily oral doses of phytonadione (vitamin K) between 2.5 and 5.0 mg have kept her protime/international normalized ratio (PT/INR) in the normal range. She has not required vitamin D supplementation beyond what was contained in MVI, likely because she has always lived in sunny environments.

DISCUSSION

Information about infants with rare ABL and the related conditions is limited (13). Untreated or undertreated patients typically developed neurological and/or retinal manifestations by the second decade, and often did not survive beyond the third decade. Some infants with ABL still struggle to find a commercial formula with a tolerable fat content to prevent diarrhea or steatorrhea, the consequences of fat-malabsorption. For those infants, a modifiable formula such as AbetaMF may provide a life-altering option (15).

The composition of AbetaMF which provides about 71 Cal/100 mL is shown in Table 3. The overall calorie make-up was 75% carbohydrate, 13% protein, and 12% fat, including EFA (1.4%

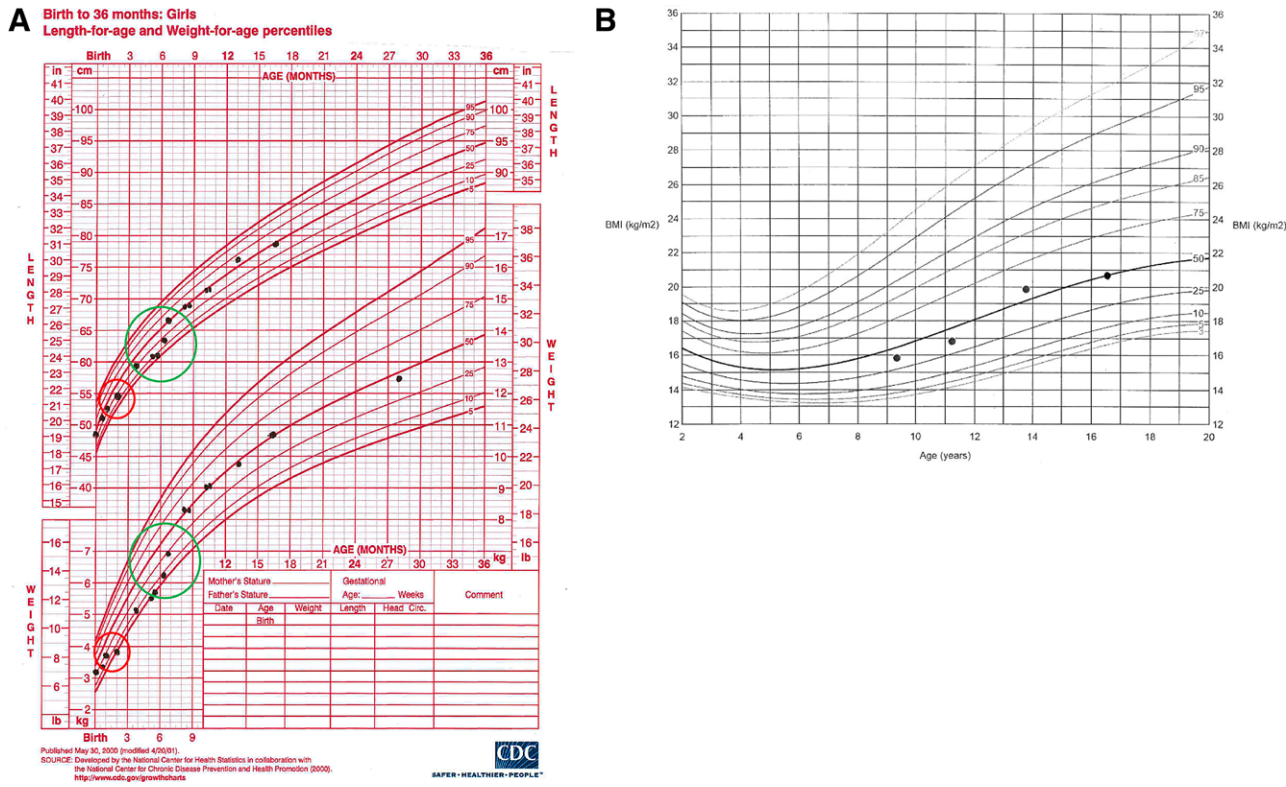

FIGURE 1. Patient's growth charts: A, The growth chart for the first 2-1/2 years of life. Red circles indicate the onset of the symptoms (failure to thrive) due to abetalipoproteinemia, and green circles indicate the positive impact of AbetaMF. Failure to thrive was becoming apparent at 2 months of age when her weight fell from 25th %ile to 5th %ile. At 6 months, both her weight and height were below 10th %ile (red circles). A positive impact of AbetaMF was clearly evident at 7 months for her length, and 8 months for her weight, both at 50th %ile (green circles). B, The body-mass-index (BMI) during childhood. Despite the rocky transition from AbetaMF to solid foods around age 5, the patient continued to grow well. Her BMI has stayed around 50th %ile, including the most recent BMI of 50th %ile at age 17 years old.

TABLE 3. AbetaMF Composition (71 Cal/100 mL, 21 kcal/oz)

	Important nutrients	Amount	Beneficial characteristics
ProViMin*	Casein (high-quality milk protein)	28 g	1. ProViMin is fully fortified with vitamins and minerals as well as adequate amounts of electrolytes for infants. 2. ProViMin also provides more than enough protein (at least 2 g of protein/kg). 3. The amount of essential fatty acids is fully maximized. AbetaMF provides more than the amount of essential fatty acids specified by the guidelines (at least 0.5%–1% of alpha-linolenic and 3%–5% of linoleic acids).
Polycose*†	Glucose polymer module (readily digestible carbohydrate)	128 g	
Corn oil	13% saturated fat 1% alpha-linolenic 57% linoleic acids 29% oleic acids	7 mL	
Flaxseed oil	9% saturated fat 57% alpha-linolenic 16% linoleic 18% oleic acid	2 mL	
Water			
Total volume		~860 mL (~29 fl oz)	

AbetaMF (a modular formula for abetalipoproteinemia).

An older modular formula (15) consisted of 2 g Vitapro (no detailed information currently available), 15 g glucose polymer, and water to the total of 100 mL and consisted of 89% carbohydrate 9% protein, and only 2% fat, heavily dependent on carbohydrate for energy source. The calorie composition of AbetaMF is 75% carbohydrate, 13% protein, and 12% fat (1.4% alpha-linolenic and 5.0% linoleic fatty acids).

*Abbott Nutrition, Abbott Laboratories, Columbus, OH.

†No longer commercially available (Maltodextrin power, Polycal, Nutricia Metabolics, Gaithersburg, MD, can be used as replacement).

alpha-linolenic and 5.0% linoleic). Typically, infants with ABL are unable to consume breast milk or an infant formula which supplies about 50% of calories from fat (Table 4) without having diarrhea or steatorrhea, but they are usually able to tolerate about 10% to 20%. Monogen (Nutricia, Gaithersburg, MD) and Lipistart (Nestlé, Bridgewater, NJ) not on Table 4, used for other fat-malabsorption

TABLE 4. Comparison of AbetaMF with other infant formulas (per 100 mL, based on current data)

	AbetaMF	Human, Milk*	Monogen†	Alimentum†	Neocate Infant†	Tolerex
Carbohydrate%	75	39	62	40	43	90
Protein%	13	6	12	11	11	8
Fat%	12	55	26	49	46	2
LCT (g) / % of total fat	0.94 / 100%	4.23 / 93%	0.35 / 16%	2.51 / 67%	2.31 / 67%	0.2 / 100%
MCT (g) / % of total fat	0‡ / 0%	0.33 / 7%	0.33 / 7%	1.24 / 33%	1.14 / 33%	0 / 0%
Alpha-linolenic acids (mg)	113	23.3§	28.6	—	59	0
Linoleic acids (mg)	396	53.8§	151	541	499	100
DHA (mg) / ARA (mg)	‖	11.85¶ / 23.7¶	10.1 / 10.1	5.6 / 15	11.4 / 11.4	0 / 0
Minerals (Na, K, Ca, Phos, Iron) (mg)	39, 108, 78, 55, 1.3	18, 53, 33, 15, 0.03	36, 69, 60, 36, 1.1	30, 80, 71, 51, 1.2	26, 74, 78, 55, 1.0	51, 117, 56, 56, 1.0
Osmolality (mOSM/kg water)	361	~300	235	320	360	550

Monogen, Nutricia Metabolics, Gaithersburg, MD.
Similac Alimentum, Abbott Nutrition, Columbus, OH.
Neocate Infant DHA/ARA, Nutricia North America, Gaithersburg, MD.
Tolerex Nestlé, Health Science, Bridgewater, NJ.
Comparison of AbetaMF with other infant formulas (per 100 Calories, based on current data), Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/PG9/A19.
ARA = arachidonic acids; DHA = docosahexaenoic acids; LCT = long-chain triglycerides; MCT = medium-chain triglycerides.
*Human, milk (modified with information available at https://fdc.nal.usda.gov/fdc-app.html#/food-details/781082/nutrients).
†Monogen, Alimentum, and Neocate Infant are newer formulas reformulated with DHA/ARA.
‡MCT may not be well tolerated by some infants with abetalipoproteinemia, and inconsistent findings of hepatic fibrosis have been observed (16).
‖Consider addition of DHA/ARA.
§Influenced greatly by the mother's intake.
¶Based on the data obtained from *Ann Nutr Metab* 2016;69(suppl 2):28–40.

disorders, contain large amounts of medium chain triglycerides (MCT) which may not be suitable for or well-tolerated by some infants with ABL (16,17). Newer formulas contain docosahexaenoic acid and arachidonic acid, and their addition to AbetaMF should be considered. Tolerex (Nestlé, Bridgewater, NJ), which has been formulated for patients with severely impaired gastrointestinal function, lacks balanced nutrients and is not appropriate for infants.

ABL is a rare heritable condition with extremely low TC, LDL-C, and TG levels, and severe deficiencies of fat-soluble vitamins and EFA. AbetaMF which contained most essential nutrients in addition to fat-soluble vitamin supplementation starting in infancy has been instrumental in the normal growth and development of our patient, and has helped her avoid the detrimental consequences of her disease. Therefore, a modifiable formula such as AbetaMF may also benefit other infants with ABL or a related condition. The care of such patients requires a multi-disciplinary approach, including the expertise of a metabolic nutritionist.

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