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# Case Reports

## Biotin Deficiency in a Patient with Short Bowel Syndrome during Home Parenteral Nutrition*

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**ABSTRACT.** A 54-year-old woman with short bowel syndrome was supported with home parenteral nutrition. Six months after receiving 2200 kcal/day of balanced home parenteral nutrition without biotin, she developed biotin deficiency with complete hair loss, eczematous dermatitis, waxy pallor, lethargy, and hypersthesias. Blood and urine samples were collected prior to treatment. Serum zinc was 64 μg/dl (nl 50–150 μg/dl), and the triene/tetraene ratio was 0.068 (nl 0.4), thereby ruling out zinc and essential fatty acid deficiencies. Serum biotin was 332 pg/ml (nl 520 ± 220 pg/ml), and urine biotin was 5.22 ng/mg of creatinine (nl 4.3–95 with a mean of 30.2 ng/mg creatinine). The same parenteral nutrition regimen was contained and oral biotin was administered (10 mg/day). After 3 wk, serum and urine biotin levels were 650 pg/ml and 35.6 ng/mg creatinine, respectively. New hair growth was evident and all of her other symptoms resolved. Intravenous biotin was then provided (5 mg/day) for a month after which serum and urine biotin levels were 1316 pg/ml and 178 ng/mg creatinine, respectively. The patient has been subsequently maintained on an intravenous multivitamin product containing 60 μg biotin per daily dose and remains free of signs and symptoms of biotin deficiency. (*Journal of Parenteral and Enteral Nutrition* **8**:311–314, 1984)

Biotin deficiency was first recognized in animals and later in man when fed raw egg white which contains avidin, a glycoprotein which forms an insoluble complex with biotin.[1] This deficiency was successfully reversed by dietary supplementation with biotin. Recently biotin-responsive multiple carboxylase deficiencies have been described in pediatric patients.[2,3] In addition, four case reports have described biotin deficiency in patients supported with long-term total parenteral nutrition.[4–7] The present report documents a nutritional biotin deficiency in an adult with short gut syndrome after biotin-free parenteral nutrition for 1 yr.

### CASE REPORT

A 54-yr-old married housewife was admitted to the University of Michigan Hospitals in January 1980 with acute mesenteric ischemia. Despite attempted mesenteric revascularization with an iliac-hepatic saphenous vein bypass graft, she required resection of the right colon, entire ileum, and all but the proximal 21 cm of jejunum. The jejunum was anastomosed to the mid transverse colon and she was discharged maintaining her weight on an oral diet. In August 1980, she was readmitted for correction of dehydration and malnutrition. Intravenous hydration and various diet regimens were attempted, but the patient continued to have watery stools, weight loss, and poor nutrition. Total parenteral nutrition (TPN) was initiated 10 days after admission for a period of 4 wk. During this period, she increased her weight from 36.8 to 48 kg. Weight maintenance on an oral diet was attempted again for 6 wk, but was unsuccessful. She reportedly had no raw egg white intake during this period. Her weight dropped to 37 kg, and TPN was reinstituted. After 6 more wk of hospitalization and several unsuccessful attempts at weaning to an oral diet, a Broviac catheter was placed and training for home TPN was initiated. The patient was discharged home 2 wk later on 2 liter/day of 4.25% amino acids and 25% dextrose. Five hundred ml of fat emulsion 10% (Intralipid, Cutter Laboratories, Berkeley, CA) was given twice a week. Other medications included propranolol 20 mg (Ayerst Laboratories, New York, NY) twice a day and hydrochlorothiazide 50 mg daily. The TPN solution contained the estimated daily requirements of electrolytes, trace elements, and vitamins. Biotin was not included in the vitamin supplementation commercially available at that time. Although one multivitamin product containing biotin may have been available in the market, the necessity of including biotin in the parenteral nutrition regimen was not strongly established, nor was such a product a hospital formulary item at that time. Zinc was increased

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from 4 to 8 mg/day for 1 wk because of a low serum zinc value of 23 μg/dl (nl 50–150 μg/dl). A repeated serum zinc level 1 month later was 82 μg/dl.

Eight months later, in April of 1981, the patient was readmitted to the hospital with severe abdominal pain. Arteriography demonstrated occlusion of the iliac-hepatic saphenous vein bypass. A thoracic aorta-common hepatic bypass was successfully performed. At the time of admission, the patient reported unusual hair loss every time she combed her hair. Serum zinc determination was normal. Daily zinc supplementation was nevertheless increased to 8 mg and continued for 6 wk after which it was reduced to 4 mg/day. Ten percent fat emulsion supplementation, 500 ml twice a week, was continued as before.

Postoperatively and at home, the patient continued to be lethargic, depressed, and anorexic despite restoration of her normal weight by TPN. She gradually became ataxic and developed progressive alopecia (Fig. 1). This was accompanied by eczematous dermatitis, waxy pallor, and diffuse hyperesthesias (Table I). The patient became progressively depressed. At that time, serum zinc, serum essential fatty acid, and plasma biotin levels were determined. There was no evidence for metabolic acidosis. Biotin deficiency was suspected and treatment with daily oral doses of 10 mg of biotin in a hydroalcoholic solution was started empirically and continued for 22 days. The decision to use oral biotin was made because biotin injections were not immediately available. Serum zinc was normal at 64 μg/dl, and the triene/tetraene ratio was 0.068 (normal less than 0.4) indicating that hair loss and other symptomatology was not due to zinc or essential fatty acid deficiencies. Low plasma and urine biotin levels then confirmed biotin deficiency (Table II). After 5 days of therapy, new hair growth was evident, and all of her other symptoms had improved.

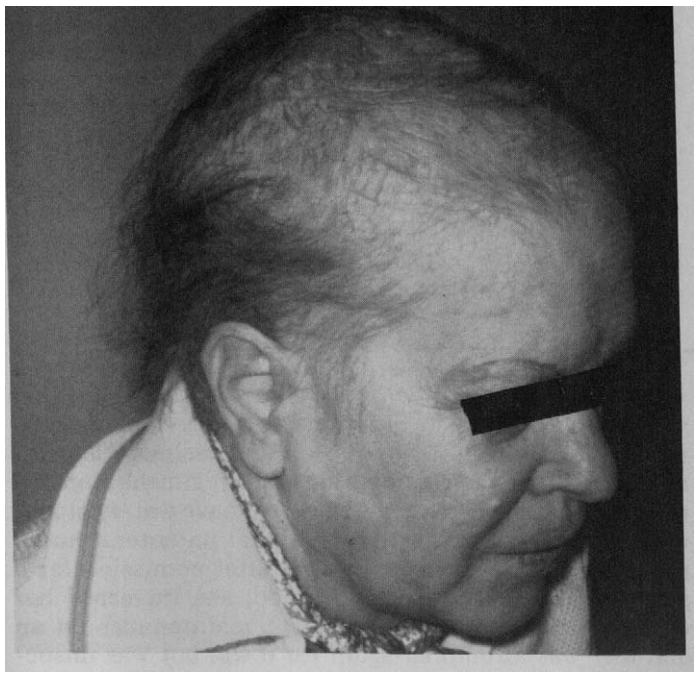

FIG. 1. The patient with biotin deficiency.

Three weeks later, parenteral biotin, 5 mg daily, was added to her parenteral nutrition solution for 4 wk, after which oral supplements of 10 mg/day were reinstituted. When high dose biotin was discontinued, the patient was begun on MVI-12 (USV Laboratories, Tuchaho, NY) in her parenteral nutrition solution supplying 60 μg of biotin per day.

She successfully maintained her weight at the ideal recommended level of 50 kg. Her hair was fully grown 6 months later (Fig. 2). She is currently active at home and exercises frequently on her bicycle, participates in social activities with her family and friends, and eats a regular diet of approximately 600–800 kcal/day. This is supplemented by 2000 kcal of parenteral nutrition 5 days a week. She continues to do well.

TABLE I
*Clinical signs and symptoms of biotin deficiency*

| |
|---|
| Depression |
| Ataxia, hypotonia, lethargy, hyperesthesias |
| Partial memory loss |
| Waxy pallor, eczematous dermatitis |
| Body hair loss |
| Anorexia |

TABLE II
*Results*[a]

| Day of treatment | 1st Day | 21st Day | 55th Day | 90th Day | Normal values |
|---|---|---|---|---|---|
| Therapy with biotin | 10 mg/day po (day 1–21) | 5 mg/day iv (day 21–55) | 10 mg/day po (day 55–90) | 0.06 mg/day iv (day 90 to present) | |
| Biotin (plasma) pg/ml | 332 | 650 | 1316 | 946 | 520 ± 220 |
| Biotin (urine) ng/mg creatinine | 5.2 | 35.6 | 178 | 9.4 | 4.3–95 mean 30.2 |
| Zinc (serum) μg/100ml | 64 | | 70 | | 50–150 |
| Essential fatty acid triene/tetraene | 0.068 | 0.072 | 0.05 | | <0.4 |

[a] Plasma and urinary free biotin concentrations were determined by a competitive protein-binding assay using $^{3}$H-biotin, avidin, and nitrocellulose filters.[8] Zinc was determined by atomic absorption spectrophotometry. The fatty acid composition of plasma lipid was determined by gas chromatography of the methyl esters formed with boron tri-fluoride and methanol (courtesy of A. N. Siakotos, Indiana University School of Medicine).

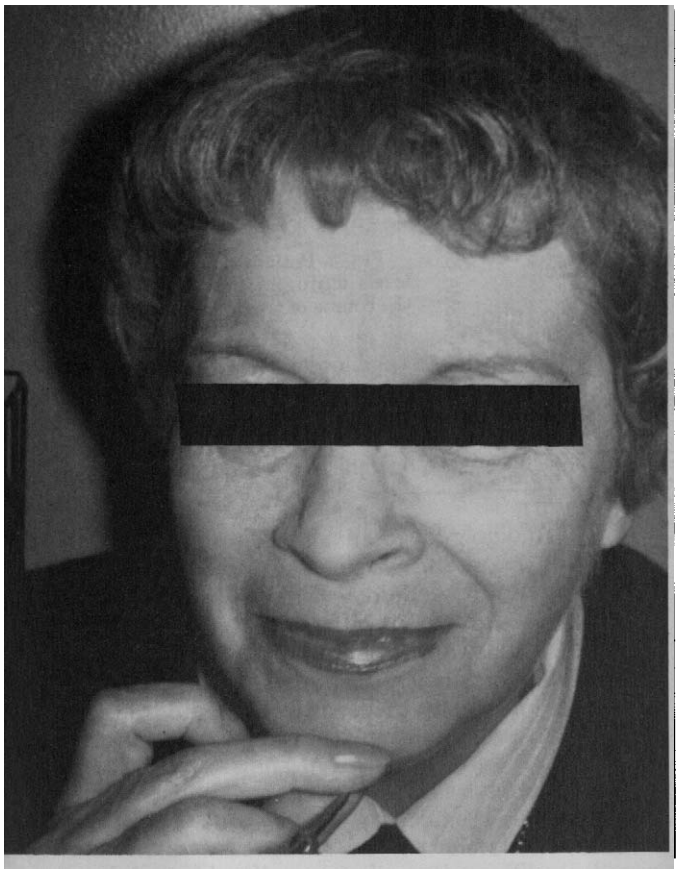

FIG. 2. The patient 6 months after treatment with biotin.

## DISCUSSION

Biotin is a coenzyme for several carboxylation reactions and plays an important role in $CO_2$ fixation. As a cofactor for both pyruvate carboxylase and acetyl co-A carboxylase, biotin plays an important role in both carbohydrate and fat metabolism.[1] Biotin deficiency is rare unless a patient is deprived of biotin in the diet, is fed raw egg white which renders biotin unabsorbable from the intestine due to the formation of an avidin-biotin complex, or unless the patient has juvenile multiple carboxylase deficiency.[2,3] Although a recommended dietary allowance for biotin has not been established, the conventional mixed American diet containing approximately 100–300 μg of biotin will meet the needs of practically all healthy adults. Probably half of the dietary biotin is absorbed from the small bowel and excreted by the kidneys in the active form.[12] Although biotin is not commercially available at the present time in a single injectable form, we have prepared a parenteral form from *d*-biotin in normal saline, autoclaved it, and demonstrated that it retains its biologic activity and stability.

Hair loss, dermatitis, and depression have been described in deficiency states of zinc,[9] essential fatty acids,[10] biotin,[1–7] and with certain drugs such as propranolol.[11] Hair loss was the first symptom noted by our patient and was progressive over a 3-month period. Despite zinc supplementation of greater than daily maintenance doses for 6 wk, she became extremely depressed, with eczematous dermatitis, waxy pallor, lethargy, and hyperesthesias. Her hair loss was almost complete. The patient's description of her deterioration was quite striking. Her mood was much more labile, and she was frequently "discombobulated." She noted her memory became very poor and her ability to perform daily functions markedly deteriorated. She had previously compounded and administered her own parenteral nutrition prescription, but became unable to do this without her husband's assistance. She completely lost her appetite for the little food she ate and she reported that everything tasted like straw during this period of time.

Because we initially suspected zinc deficiency as a cause for the patient's early symptoms of hair loss and dermatitis, zinc supplementation was increased from 3 to 8 mg/day emperically for 1 month with no clinical effect, and serum zinc levels were normal (Table II). Soy bean oil emulsion was infused twice a week in amounts that provided at least 3.2% of the patient's daily caloric intake as linoleic acid. This made essential fatty acid deficiency very unlikely, and a normal triene/tetraene ratio was confirmed by direct measurement (Table II). This left two possible etiologies for the patient's signs and symptoms: propranolol therapy and biotin deficiency. Propranolol administration may occasionally produce side effects, including fatigue, mental depression, erythematous rash, and reversible alopecia.[11] Since the patient had been successfully maintained on this drug for over 2 yr without untoward sequalae, propranolol seemed to be an unlikely etiology. Thus, a tentative diagnosis of biotin deficiency was considered and supplementation initiated. It was decided not to reverse this biotin deficiency with any of the oral biotin tablets or multivitamin products containing biotin available at that time because of the patient's short bowel. Although MVI-12 had been recently introduced on the market at that time, it contained only maintenance levels of biotin and correcting a single vitamin deficiency with a multivitamin preparation was not appropriate. Intravenous biotin of 5 mg/25 ml normal saline (*d*-biotin by Sigma Chemical Co., St. Louis, MO) was then prepared by our Pharmacy Laboratory. Sterile-autoclaved biotin solution was analyzed and found to retain its activity and stability; oral doses of 10 mg in a 15 ml 60% ethanol cherry-flavored solution were also prepared for immediate use until the intravenous products were tested for sterility and analyzed for activity. Sixty percent ethanol was used as the solubilizing agent because biotin is more soluble in alcohol (80 mg/100 ml of 95% alcohol) than water (22 mg/100 ml), and we rationalized that a rapid absorption of ethanol might enhance the rate of absorption for biotin in this patient with short bowel syndrome. The same parenteral nutrition regimen was maintained as before, and propranolol administration was also continued, so that the only change in the patient's daily regimen was the addition of biotin.

The patient reported a euphoric state upon the initial administration of biotin, presumably because of the alcohol content. On the 5th day of treatment, she reported general overall improvement in her clinical state including improvement of her depression, hyperesthesias, and

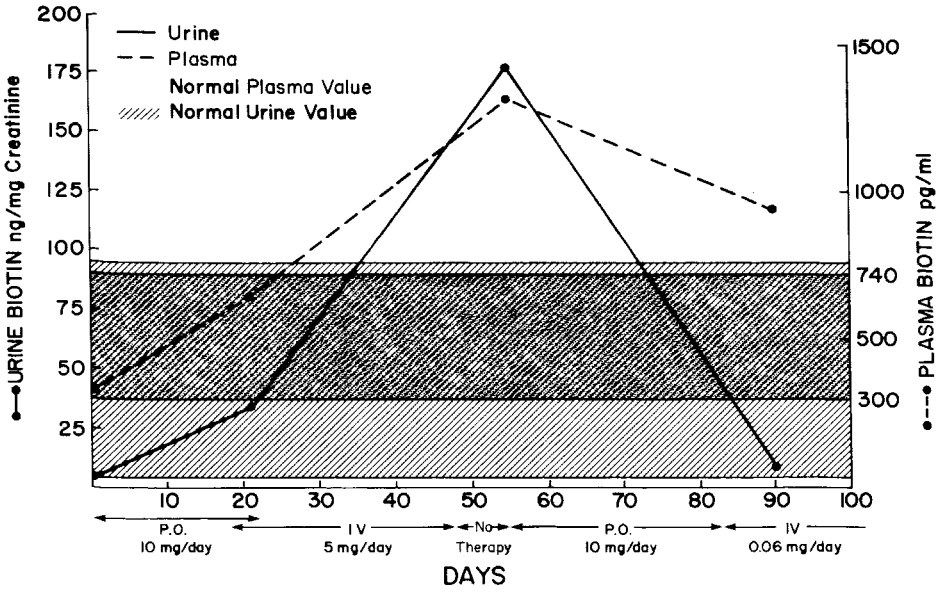


FIG. 3. Patient's plasma and urine biotin levels during biotin deficiency and during the course of treatment with biotin.

lethargy. She noted the growth of new hair on her scalp and elsewhere on her body and her hair had returned to normal length 6 months later.

The patient's initial serum and urinary biotin concentrations were in the low normal range (Fig. 3). Her plasma concentration was 1 SD below the mean, and her urinary biotin excretion was almost 2 SD below the mean. The rapid response of her symptoms to biotin therapy as well as the increase in both plasma and urinary biotin concentrations makes biotin deficiency the likely cause of her pallor, ataxia, and alopecia.

We speculate that this patient's short bowel may have contributed to the development of the biotin deficiency as hypothesized by others.[1] The short bowel may have decreased transit time, thereby reducing the chance of adequate absorption from the little food she ate. Moreover, we further speculate that the broad spectrum antibiotics which this patient was on may have altered the intestinal flora and therapy decreased biotin production by micro-organisms.

Table II shows that intravenous administration of one-half of the oral biotin dose gave higher levels in the serum and urine compared to the oral regimen. Both regimens, however, were at greater than maintenance level, and probably one-half of the oral dose or one-tenth of the intravenous dose would have effectively reversed the symptoms of biotin deficiency. Therefore high doses, such as those used in pediatric patients with biotin-responsive multiple carboxylase deficiency, probably need not be given to patients with a straight forward dietary deficiency. During the past year, our patient has been supplemented daily with 1 mg biotin orally and 60 μg intravenously. In January 1983, her plasma biotin was 411.9 pg/ml and urine biotin was 13.3 ng/mg of creatinine. Both values are in the low-normal range suggesting that a daily biotin supplementation of 60 μg intravenously, as now provided in commercial multivatimin preparations, may not be sufficient for all patients.

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