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# Clinical Findings in Four Children with Biotinidase Deficiency Detected through a Statewide Neonatal Screening Program

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# CLINICAL FINDINGS IN FOUR CHILDREN WITH BIOTINIDASE DEFICIENCY DETECTED THROUGH A STATEWIDE NEONATAL SCREENING PROGRAM

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**Abstract** Four children with biotinidase deficiency were identified during the first year of a neonatal screening program for this disease in the Commonwealth of Virginia. Two unrelated probands were identified among the 81,243 newborn infants who were screened. In addition, two siblings of one of these infants were found to be affected. Both probands had mild neurologic symptoms at two and four months, respectively, and the two older children had more severe neurologic abnormalities, cutaneous findings, and developmental delay at two and three years of age. However, none of the affected children had acute metabolic decompensation. Previous studies have shown that the administration of biotin to affected children can be a lifesaving procedure that can reverse acute symptoms and prevent irreversible neurologic damage. Our findings demonstrate that subtle neurologic abnormalities may appear as early as at two months of age and that developmental abnormalities may occur even in the absence of episodes of overt metabolic decompensation. Since screening and treatment are both inexpensive and effective and the incidence of the disease is well within the range of that of other metabolic diseases for which screening is performed, biotinidase deficiency should be added to the group of metabolic diseases for which screening is done in the neonatal period. (N Engl J Med 1985; 313:16-9.)

BIOTINIDASE deficiency is an autosomal recessive disorder in which there is an inability to cleave biotin from biocytin or other biotinylated peptides resulting from the degradation of endogenous carboxylases and an inability, therefore, to recycle the vitamin biotin.[1,2] Patients with this disease may ultimately become biotin deficient during infancy or early childhood and have one or more of the following signs and symptoms: seizures, skin rash, alopecia, ataxia, hearing loss, developmental delay, or metabolic decompensation that can terminate in coma and death.[3] Affected infants do not have abnormalities at birth, and all symptomatic patients treated thus far have improved markedly after the administration of pharmacologic doses of biotin. In some cases, biotin sup-

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plementation has been lifesaving, and if appropriate treatment is delayed, irreversible neurologic damage may develop. Since the disease can be detected by a simple screening test and the treatment is inexpensive and effective, biotinidase deficiency meets all the major criteria for a disease for which neonatal screening should be performed.[4] In this report, we describe the clinical findings in four affected patients who were identified through a year-long pilot screening program in the Commonwealth of Virginia that was initiated to determine the incidence of biotinidase deficiency at birth and the cost effectiveness of screening.[5] The diagnosis of biotinidase deficiency was confirmed in 2 of 81,243 newborn infants screened. Both infants had similar mild neurologic findings at the time of detection and were promptly started on biotin treatment. In addition, two secondary cases, both with definite cutaneous and neurologic abnormalities but not metabolic disturbances, were identified among the siblings of one proband.

## Methods

Biotinidase activity was determined by a semiquantitative colorimetric method on the dried-blood–impregnated filter papers that are used for neonatal metabolic screening.[6] When the blood spot is incubated with the substrate and subsequently with the color-development reagents, samples with biotinidase activity have a distinct purple color, whereas those with deficient enzyme activity remain straw-colored. A quantitative colorimetric assay for biotinidase activity in serum was used to confirm positive screening tests and to identify heterozygotes.[2] The presence of organic acids in the urine was determined by the method of Goodman and Markey.[7]

## Case Reports

### Patient 1

The proband was a 3.64-kg (80th percentile) baby girl born after a 38.5-week gestation to a 25-year-old white, gravida II, para II mother. The baby was 53.3 cm long (90th percentile) and had a head circumference of 35 cm (60th percentile). The pregnancy, labor, and delivery were uncomplicated. The mother took no vitamin supplements during her pregnancy. Both parents' families had lived in the same geographic area for four generations; nevertheless, we were unable to document consanguinity. The baby was reported to have a voracious appetite. She was fed Enfamil or Enfamil with iron from birth, cereals at about 1 month of age, and strained vegetables and fruits at 3½ months of age. She was not given vitamin supplements.

The results of repeated screening tests were abnormal, and biotinidase deficiency was confirmed by a finding of approximately 5 per cent of the mean normal activity in the patient's serum (0.3 nmol of para-aminobenzoate formed per minute per milliliter of serum). The mean (±S.D.) normal activity is 6.5±0.8 nmol per minute per milliliter of serum (n = 212), with a range of 4.5 to 11.0. As shown in Figure 1A, other members of the family were also found to be heterozygotes, and the gene for the deficiency appeared to have been inherited from the two grandfathers.

On physical examination when the patient was four months of age, the only abnormalities detected were a slight hypertonia, and brisk deep-tendon reflexes bilaterally. Her weight was 7.6 kg (95th percentile, or 50th percentile for a six-month-old), her length 68 cm (>95th percentile, or 50th percentile for an eight-month-old), and her head circumference 43.5 cm (>95 percentile, or 50th percentile for a 7.5-month-old). She had no cutaneous abnormalities except that her scalp hair was very fine. This pattern was reportedly similar, however, to that of her heterozygote brother at the same age. Her developmental milestones, serum electrolyte levels, and lactate concentrations were normal, and she did not have organic aciduria. The electroencephalogram was normal, and although auditory evoked responses were normal in the suprathreshold range, they were abnormal at and below the normal stimulus threshold. After completion of the diagnostic tests, daily treatment with 10 mg of biotin was begun. During the subsequent three months the parents reported that the infant was more alert and had a decreased appetite and more abundant hair.

### Patient 2

The proband was a full-term, 3.52-kg (50th percentile) baby boy born to a 33-year-old white, gravida VII, para VI mother who had had one abortion. The baby was 53.3 cm long (90th percentile) and had a head circumference of 33.5 cm (40th percentile). The pregnancy, labor, and delivery were uncomplicated. The mother took unspecified vitamins sporadically during the pregnancy. The baby was breast-fed initially but required supplementation with ProSobee at three weeks and Enfamil with iron at five weeks. He was started on rice cereal at four weeks of age and fruits at six weeks of age. He was given no vitamin supplements. The mother reported that at three weeks of age the child had an episode of "jerking" movements while asleep, during which he could not be easily aroused, but he had no fever, cyanosis, eye-rolling, or incontinence during that episode. After several minutes he awoke spontaneously.

As in the first patient, no biotinidase activity was detectable on the initial or repeated screening tests. Confirmation of biotinidase deficiency was made by the finding of deficient biotinidase activity in the patient's serum (0.26 nmol per minute per milliliter of serum, or 4 per cent of the mean normal activity). Figure 1B shows the pedigree of this family. The gene for the deficiency can be traced to the maternal grandmother and the paternal grandfather.

When the infant was two months of age, physical examination revealed that his weight was 5.82 kg (95th percentile), his length 58 cm (75th percentile), and his head circumference 39.5 cm (60th percentile). He was hypertonic, with brisk deep-tendon reflexes but no clonus. There were no cutane-

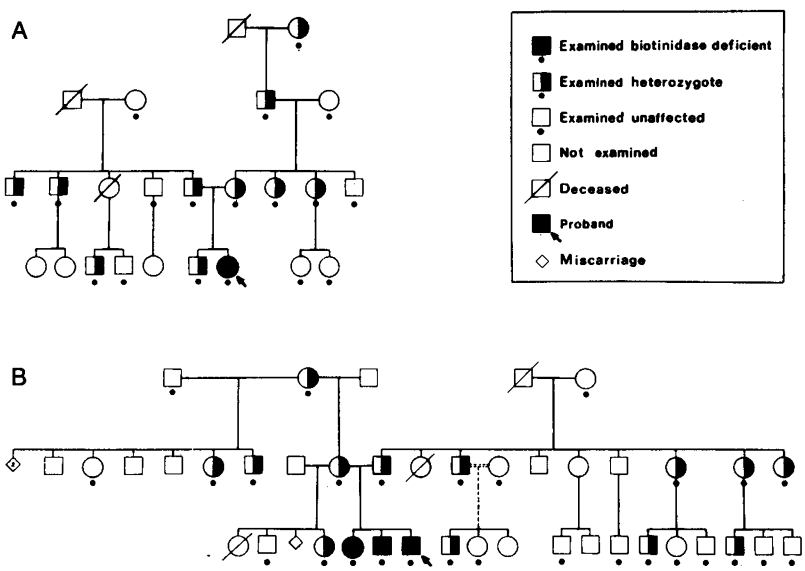


Figure 1. Family Pedigrees of Infants Identified in Newborn Screening As Having Biotinidase Deficiency.

ous findings, with the exception of a uniform sparseness of scalp hair. The child's activity and developmental milestones and his serum electrolyte, lactate, and pyruvate concentrations were all normal, and he had no organic aciduria. The electroencephalogram and auditory evoked potentials were also normal. On the basis of the neurologic findings, the infant was treated with 10 mg of biotin per day. A follow-up examination after three weeks of biotin treatment revealed a marked decrease in hypertonia, but the brisk reflexes persisted. The mother reported that he was less irritable and that his appetite had decreased. As in the first patient, thick hair was growing in.

### Patient 3

This child was the 3¼-year-old sister of Patient 2, who was found to have biotinidase deficiency during the follow-up testing of the relatives of Patient 2 to determine their carrier status. Biotinidase activity was 0.17 nmol per minute per milliliter of serum. At birth after a full-term pregnancy, she weighed 3.14 kg (45th percentile) and was 52 cm long (75th percentile); the pregnancy, labor, and delivery were uncomplicated except for a "knotted" umbilical cord and a mild cephalohematoma. An apparent transient tachypnea developed, but the infant was discharged home in two days. During the pregnancy and lactation, the mother took iron and vitamin supplements containing no biotin. The infant was breast-fed for six weeks, but because of her voracious appetite, she was switched to ProSobee. Fruits and rice were added to the diet at four weeks, vegetables at two months, and meats at six months of age. The child was not given vitamin supplements. She had no hair at birth; her hair began to grow at nine months. Thrush developed when she was six weeks old and lasted for one month even with therapy, and she had frequent ear infections. During the first two years she attained normal developmental milestones; however, in the six months before we tested her, the parents had noticed that her speech, which was previously articulate, had become "slurred." Physical examination revealed a slight atopic, dermatitis-like rash on her cheeks and a mild seborrheic rash around her eyebrows. The growth rate and distribution of her hair were normal. Neurologic examination revealed immature enunciation and articulation, slight hypotonia, and delayed gross and fine motor function. The deep-tendon reflexes were normal, but there was a mild intention tremor and a slight degree of clumsiness. Gross and fine motor control, cognitive skills, and language as assessed by the Gesell test were in the normal range for children 2½ to 3 years old. Personal and social skills were slightly advanced — at the 3½-to-4-year level. Overall assessment of the child found her to be in the low-normal range. The serum electrolyte and lactate concentrations were normal, and no abnormal organic aciduria was detected. The results of electroencephalography and auditory evoked-potential studies were normal. After this evaluation the patient was treated with 10 mg of biotin per day.

### Patient 4

This child was the 2¼-year-old affected brother of Patients 2 and 3. His serum biotinidase activity was 0.19 nmol per minute per milliliter of serum. He was born at full term after an uncomplicated pregnancy, labor, and delivery; at birth he weighed 3.44 kg (50th percentile) and was 53.3 cm long (85th percentile). He was breast-fed for the first six weeks, when he was switched to ProSobee because of an insatiable appetite. He was given fruit and rice cereal at four weeks, vegetables at two months, and meats at six months. He received no vitamin supplements. At birth he had fine black hair, which he lost between the ages of two and four weeks. His hair returned at about nine months of age. At four weeks of age he had thrush, which took several weeks to clear after nystatin therapy, and he has continued to have frequent ear infections. During the three months before we saw him he had had four or five episodes of hand swelling and itching, which subsided spontaneously. He achieved normal developmental milestones, except for delayed speech. He spoke his first word at 11 months and at age 2¼ was just beginning to speak in sentences. Physical examination showed a moderate atopic, dermatitis-like rash with a telangiectatic appearance on the child's cheeks, dry excoriation around his nose and chin, and a seborrheic rash around his eyebrows. He was more hypotonic than his sister and had a mild hand tremor. He walked with a wide-based gait and had slightly flat feet. According to the Bayley Scales of Infant Development, he had decreased vocabulary and speech articulation for his age. He had delayed gross and fine motor skills, but no tremors. He scored 77 in mental development and 66 in psychomotor development, yielding an overall assessment in the borderline-normal range. Serum electrolyte and lactate concentrations were normal, as was the urinary organic acid profile. The results of electroencephalography and auditory evoked-potential studies were normal, although the child had mildly increased impedance in his left ear due to a serous otitis media infection. On the basis of these findings he was also treated with 10 mg of biotin per day.

## Discussion

Because the screening program was a pilot project and was conducted in a separate laboratory, we did not have access to the efficient follow-up procedures that have been developed for the existing statewide metabolic-screening program. Consequently, we experienced considerable delay in obtaining follow-up samples, and the diagnosis in the first affected proband was not confirmed until the child was four months of age. However, the diagnosis was confirmed in the second proband by the age of two months, and more rapid confirmation would be anticipated if the test were incorporated into the routine screening program. As is not the case in some metabolic diseases, unequivocal confirmation of the diagnosis can be accomplished readily by quantitative determination of serum biotinidase activity as well as by documentation of half the normal enzyme activities in the heterozygous parents. The testing of members of the family of Patient 2 unexpectedly revealed that both full siblings of the proband were deficient in biotinidase. The subtlety of their behavioral and neurologic abnormalities would have made a diagnosis of biotinidase deficiency unlikely on routine examination.

The phenotype in biotinidase deficiency appears to be quite variable, and the causes of this variation are not completely understood. Some children have had neurologic symptoms without cutaneous findings or organic aciduria.[3,8] Both the biotinidase-deficient infants in this study already had mild, somewhat similar neurologic findings at the time of detection. In addition, the two-month-old child may have had a seizure at about three weeks of age, and the four-month-old infant had abnormal auditory evoked potentials. However, the clinical abnormalities in these infants were so subtle and nonspecific that they clearly could not have been relied on to suggest the presence of a metabolic abnormality in the absence of a positive screening test. In time, however, other neurologic or cutaneous manifestations of the disease might have developed. The two older children, for example, had definite neurologic abnormalities, developmental delay, and persistent oral monilial infections, perhaps due to abnormalities in cellular immunity similar to those that have been described in several other children with biotinidase deficiency.[9,10] However, none of the four affected children had metabolic disturbances such as organic aciduria. Because of the clinical vari-

ability of this disorder, affected children may not be found to have remarkable abnormalities on routine examinations, even when conventional metabolic tests are performed.

The parents of these four children reported them to have been colicky feeders; the three children from the second family were all initially breast-fed but could never be satiated. Other parents have also reported polyphagia in their affected children during the newborn period, and it may be that their insatiable appetites reflect a physiologic attempt to satisfy the need for a limiting nutrient. All four affected children were fed formula by six weeks of age. Because of losses of low-molecular-weight constituents during the dialysis involved in their preparation, these formulas are required by law[11] to be supplemented with a minimum of 1.5 μg of biotin per 100 kcal. Cow's milk contains twice the biotin in human milk,[12] and formulations based on whole or defatted (skim) milk need not be fortified with biotin. Breast-fed infants and infants consuming formulas supplemented at the minimal level would consume 6 to 10 μg of biotin daily. This is well below the suggested safe intake (no recommended daily allowance has been determined) of 35 μg per day.[13] However, Enfamil and ProSobee, the products used by these biotinidase-deficient children, contain more than the minimal requirement (2.3 and 7.8 μg per 100 kcal, respectively), and children consuming these products would be receiving considerably more biotin.

Our findings suggest that biotinidase may be necessary to liberate biotin from various dietary sources, and we have proposed that biotinidase-deficient persons may require their biotin in the free form.[14] Perhaps some of the clinical variability in this syndrome may be attributable to differences in the quantities of free biotin in the diets. Since the children described here were only mildly symptomatic, it is possible that their intake of free biotin was sufficient to prevent the development of acute metabolic decompensation, but suboptimal for normal neurologic development. Under the stress of fever, injury, infection, starvation, or possibly, rapid growth, their capacities for maintenance of homeostasis could be exceeded, and acidosis and possibly coma or death might result. Although recommendations of safe intakes of biotin have been made for normal infants, no recommended daily allowance has been established. This is largely because the magnitude of the contribution of the gastrointestinal microflora is unknown. Clearly, there is a small subpopulation of children who require more free biotin for normal development, and since the therapeutic doses of biotin used to treat biotinidase-deficient persons are not toxic, a reassessment of the biotin requirements for infants seems appropriate.

Two of the affected infants in this study were found among the 81,243 newborns screened during the first year of the program. The incidence of biotinidase deficiency can thus be estimated to be about 1 in 41,000 newborns, with 95 per cent confidence limits of 1 in 12,000 to 1 in 240,000. This estimate places the incidence of biotinidase deficiency well within the range of that of other metabolic disorders that are currently being tested for in many screening programs.[15] Our results indicate that the semiquantitative colorimetric screening test is a feasible method of screening for this disorder. Although much remains to be learned about the natural history of biotinidase deficiency, our experience with patients identified through the newborn-screening program demonstrates that the presence of either overt clinical abnormalities or metabolic decompensation cannot be relied on for early diagnosis. Biotinidase deficiency thus meets all the recognized criteria for a disease for which neonatal screening should be performed.

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