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INBORN ERRORS OF BIOTIN METABOLISM*
Clinical and Laboratory Features of Eight Cases

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There are two genetically determined biotin-dependent disorders. The first is holocarboxylase synthetase (HCS) deficiency and the second biotinidase deficiency. HCS catalyzes the reaction in which active holocarboxylases are synthesized from inactive apocarboxylases. Biotin is required for this synthesis. Biotinidase facilitates the release and recycling of free biotin. Deficiency of either HCS or biotinidase is characterized by certain neurological, cutaneous and biochemical abnormalities.

In this paper, six patients with biotinidase and two patients with HCS deficiency are described. Among the most common neurological findings were hypotonia (6/8), seizures (2/6) and optic atrophy (2/8). Dermatitis and conjunctivitis were present in three and four patients, respectively. All patients had low blood pH bicarbonate levels. Serum lactate was increased in all and pyruvate in six cases. Two patients with biotinidase deficiency presented earlier than the mean age of onset previously reported in the literature.

Detection of eight cases during the past few years at a single metabolic unit indicates that biotinidase deficiency is not rare in Turkey, where the frequency of some other metabolic disorders has also been reported to be high. We suggest that biotin-dependent disorders should be considered in all infants with neurological symptoms, particularly those with jerks, even if other signs such as alopecia, seborrheic dermatitis and acidosis are not evident, regardless of the age of presentation. *Key words: biotin-dependent disorders, holocarboxylase synthetase deficiency, biotinidase deficiency.*

Biotin is a water-soluble, B-complex vitamin that acts as a cofactor for four mammalian carboxylases: pyruvate carboxylase, acetyl CoA carboxylase, propionyl CoA carboxylase and 3-methyl crotonyl CoA carboxylase. Biotin binds covalently to the apoprotein of these carboxylases in order to render them active in a reaction catalyzed by holocarboxylase synthetase (HCS). The active holocarboxylases are degraded by proteases in the course of normal cellular turnover. The end-products of this degradation reaction are not amino acids, unlike the situation with other proteins. The reaction is stopped when it reaches the small peptide biocytin (biotinyl-lysine) that contains biotin. Biotinidase is an

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enzyme found in serum and most body tissues, and is essential for the release of biotin from biocytin and for the recycling of free biotin. Deficiency of either HCS or biotinidase results in malfunction of all carboxylases and in organic acidemia[1-3].

In this report, we describe the clinical and laboratory features of eight cases (six with biotinidase deficiency and two with HCS deficiency) in order to draw attention to the facts that the clinical expression of biotin-dependent disorders varies and it is no longer tenable to differentiate biotinidase deficiency from HCS deficiency simply based on the relatively later age of onset of the former.

Case Reports

Clinical and laboratory features are summarized in Tables I and II. Of the following eight cases, three (Cases 1, 3 and 4) have previously been reported elsewhere[4,5].

Table I: Clinical Characteristics of Six Patients with Biotinidase Deficiency and Two Patients with Holocarboxylase Synthetase Deficiency

	Biotinidase-Deficient Cases						Holocarboxylase Synthetase Deficient Cases	
Clinical Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age of onset	30 mos	18 mos	91 days	70 days	6 mos	Newborn	5.5 mos	3.5 mos
Sex	F	M	M	F	M	M	M	F
Consanguinity	—	—	+	+	+	—	—	—
Hypotonia	—	—	+	+	+	+	+	+
Seizures	—	—	+	+	—	—	—	—
Dermatitis	+	+	+	—	—	—	—	—
Alopecia	+	+	+	+	+	—	+	—
Conjunctivitis	+	+	+	—	+	—	—	—
Optic atrophy	—	—	+	—	+	—	—	—
Stridor	+	—	—	—	—	—	—	—
Biotin treatment (mg / day)	Init. 20 Maint. 5	Init. 20 Maint. 5	Init. 10 Maint. 5	Init. 10 Maint. 5	Died before specific diagnosis	Died before specific diagnosis	Init. 20 Maint. 40	Init. 20 Maint. 40
Follow-up	doing well at 5.5 yrs	had only gait problems at 3.5 yrs	doing well at 11 mos with abnormal BAEP	doing well at 10 mos	died at 6 mos	died on the 13th day	doing well at 3 yrs	lost to follow-up

M: male, F: female, Init.: initial, Maint.: maintenance, Yrs: years, Mos: months.

Table II: Laboratory Characteristics of Six Patients with Biotinidase Deficiency and Two Patients with Holocarboxylase Synthetase Deficiency

	Biotinidase-Deficient Cases						Holocarboxylase Synthetase Deficient Cases	
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Blood pH	7.35	7.42	7.25	6.98	7.31	7.32	7.30	7.31
HCO_3	14.20	13.50	7.30	3.40	8.80	14.10	13.20	12.00
LA (mg / dl)	41.80	65.00	94.30	79.30	72.00	28.10	45.80	32.00
PA (mg / dl)	1.60	4.00	6.00	5.60	2.80	1.00	1.30	0.78
NH_3 (microg / dl)	50.00	60.00	84.00	118.00	53.80	180.00	140.00	152.00
Amino acids								
serum	Alanine ↑	Alanine ↑	Alanine ↑	N	N	N	N	N
urine	Alanine ↑	Alanine ↑	Alanine ↑	Alanine ↑	N	N	N	N
Organic acids in urine	ND	ND	typical for a biotin depend. disord.	ND	typical for a biotin depend. disord.	typical for a biotin depend. disord.	typical for a biotin depend. disord.	typical for a biotin depend. disord.
EEG	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal	ND	ND
CT	ND	N	ND	N	Abnormal	ND	ND	ND
MRI	ND	N	ND	N	ND	ND	Abnormal	N
VEP	Abnormal	Abnormal	Abnormal	Normal	ND	ND	ND	ND
BAEP	N 5.5 yrs	Abnormal problems at 3.5 yrs	Abnormal 11 mos with abnormal BAEP	Abnormal 10 mos	ND	ND day	ND 3 yrs	ND

LA: lactic acid, PA: pyruvic acid, EEG: electroencephalogram, CT: computerized tomography, MRI: magnetic resonance imaging, VEP: visual evoked potentials, BAEP: brainstem evoked potentials, N: normal, ND: not done, Depend.: dependent, Disord.: disorder.

Case 1

A 30-month-old girl was admitted to our hospital because of acute spastic laryngitis. At 10, 18 and 29 months of age, she had developed a noisy breathing pattern diagnosed as bronchitis, which persisted for several weeks. She had developed erythematous skin lesions involving the whole body and lost her hair seven months and 20 days prior to her admission to the hospital, respectively. Her parents were nonconsanguineous, and one elder sister had been healthy.

On physical examination, the patient was severely ill and had dyspnea with a respiratory rate of 46 / min, hoarseness and inspiratory stridor. Her hair texture was sparse, with the occipital region being totally alopecic. There was bilateral blepharoconjunctivitis.

Laboratory investigations revealed a metabolic acidosis (blood pH 7.35 and bicarbonate 14.2 mmol / L). Lactic and pyruvic acidemia were found (lactic acid

41.8 mg / dl, normal 10-14 mg / dl; pyruvic acid 1.6 mg/ dl, normal 0.5-1.0 mg / dl), associated with increased serum and urine concentrations of alanine demonstrated by paper chromatography. Blood ammonia was 50 µg / dl (normal 20-120 µg / dl). Upon testing with Bayley's scale, the patient was found to be slightly retarded. An electroencephalogram (EEG) displayed paroxysmal abnormalities, while visual evoked potentials (VEP) showed prolonged latencies.

Organic pathology of the larynx was excluded by direct laryngoscopy. Biochemical abnormalities coupled with neurological and cutaneous findings suggested biotinidase deficiency, and biotin was administered orally (20 mg / day in two divided doses). Both respiratory and metabolic abnormalities were normalized within three hours of initiating therapy. Biotinidase activity in whole blood was subsequently shown to be deficient. The biotin dose was gradually decreased to 5 mg / day. When last seen, the patient was 5.5 years of age and symptom-free.

Case 2

An 18-month-old boy was referred to our hospital because of respiratory difficulty and unconsciousness after having been hospitalized for about 22 days with the diagnosis of encephalitis at another institution. His parents were nonconsanguineous. An eight-month-old female sibling had reportedly been healthy.

On examination, seborrheic-type dermatitis involving mainly the perianal and gluteal area was detected. The patient had very little hair and bilateral blepharoconjunctivitis. He was responsive to painful stimuli.

Laboratory investigations revealed a blood pH of 7.42 and bicarbonate 13.5 mmol / L. Both serum lactate (65 mg / dl) and pyruvate (4.0 mg / dl) were elevated. Blood ammonia was normal (60 µg / dl). Alanine concentration was increased in serum and urine samples. An EEG showed diffuse irregular slow activity. Prolongation of latencies was detected on VEP and brainstem auditory evoked potential (BAEP) studies. Computed tomographic scan (CT) and magnetic resonance imaging (MRI) of the brain were interpreted as normal. Biotinidase activity in serum was found to be absent.

A diagnosis of acrodermatitis enteropathica was considered, but normal serum zinc concentrations made this possibility unlikely. Biotin therapy (20 mg / day in two divided doses) was initiated, and the patient responded dramatically within hours. Blood pH and bicarbonate returned to normal and the patient regained consciousness. The dermatitis and conjunctivitis disappeared within 10 days.

When last seen, the patient was 3.5 years old and doing well under biotin therapy (5 mg / day). Neurological examination still revealed weakness in the lower extremities and gait disturbance. Repeated VEP and BAEP studies gave normal results.

Case 3

A 91-day-old male infant was brought to our hospital with the chief complaints of difficulty in feeding and a generalized squamous rash. The patient had started experiencing tonic-clonic muscle jerks when he was one month old, and these had increased in frequency and severity with time. Infantile spasms were diagnosed at another institution, and he was given corticotropin and phenobarbital with some relief. Ten days after discharge, the patient was admitted to our hospital. His parents were first-degree relatives. One sibling had died at the age of five months after persistent convulsions.

On examination, lethargy, hypotonia, hyperpnea and frequent muscle jerks were noted. Generalized alopecia of the scalp and seborrheic dermatitis were also evident. Ophthalmologic examination revealed optic atrophy and keratoconjunctivitis of both eyes.

Laboratory investigations revealed a blood pH of 7.25 and bicarbonate 7.3 mmol /L. Serum lactic (94.3 mg / dl) and pyruvic (6.0 mg / dl) acid levels were increased. Blood ammonia was 84 µg / dl. Alanine concentration was increased in serum and urine samples. BAEP showed no response on the left side and only a low amplitude response on the right side. VEP showed prolonged P1 latencies on both sides. EEG showed the presence of a multifocal epileptiform abnormality. Gas chromatography-mass spectrometry (GC-MS) analysis of the urine sample was found to be typical for a biotin-dependent disorder.

A presumptive diagnosis of biotinidase deficiency was made, and biotin therapy was initiated (10 mg / day). The patient's condition responded dramatically to the administration of biotin. Blood pH and bicarbonate values were normalized within six hours. The seborrheic dermatitis improved shortly after treatment and disappeared at the end of 10 days. Biotinidase activity was later shown to be absent.

On follow-up examination at 11 months of age, the patient was doing well and had not experienced any convulsions while receiving biotin (5 mg / day). Neurological examination revealed no abnormalities.

Case 4

A 70-day-old female infant was referred to our hospital because of intractable convulsions. She began having jerky movements at one month of age. She was

hospitalized at another institution and given phenobarbital and sodium valproate, which had no effect on the convulsions. The diagnosis of infantile spasms was then made, and corticotropin was started. The frequency of convulsions decreased under such therapy, and the patient was referred to our hospital for further evaluation. The parents were third-degree relatives and had a nine-year-old healthy daughter.

Physical examination revealed a lethargic and hypotonic child with sudden jerky movements of the limbs. Scalp hair was sparse. She developed acidotic respirations on the tenth day of hospitalization.

Laboratory investigations revealed the following: blood pH 6.98 and bicarbonate 3.4 mmol / L; increased serum levels of lactic (79.3 mg / dl) and pyruvic (5.6 mg / dl) acid; and serum ammonia level of 118 µg / dl. BAEP showed no response on either side, and VEP studies were normal. EEG showed a generalized chaotic baseline pattern and paroxysmal activity in the left hemisphere. CT and MRI of the brain were both normal. The urine alanine level was increased.

Biotinidase deficiency was considered as a diagnostic possibility, and biotin was administered orally (10 mg / day), resulting in abatement of the acidosis within hours.

On follow-up examination at 10 months of age, the patient's physical and neurological findings were normal while receiving 5 mg / day biotin. The patient is currently receiving no anticonvulsant drug and is free of convulsions. A repeat BAEP was found to be unresponsive on the left side, while only a low-amplitude response could be obtained on the right side.

Case 5

A six-month-old male infant was brought to our hospital because of hypotonicity since birth. His developmental milestones were delayed. The parents were first-degree relatives, and their first three children had died of unknown causes between one and two months of age. They also had three healthy children.

On examination, the patient was generally unresponsive, not fixing or following, and was profoundly hypotonic. His hair was sparse, thin and fragile. Bilateral optic atrophy and keratoconjunctivitis were also noted.

An EEG revealed a diffuse bioelectrical abnormality with paroxysmal activity which was more marked in the left hemisphere. A CT scan revealed severe atrophy of the cerebral and cerebellar hemispheres, and dilatation of the third and lateral ventricles. Blood lactate and pyruvate concentrations were both elevated (72 and 2.8 mg / dl, respectively). Blood ammonia was normal (53.8 µ / dl). Blood pH was 7.31 and bicarbonate 8.8 mmol / L. Serum and urine amino acid patterns and immunological studies were found to be normal.

The absence of developmental progress from birth in the presence of lactic acidosis suggested a defect in pyruvate metabolism. The patient died on the tenth day of hospitalization despite all supportive measures. Urine organic acids collected just before his death revealed a pattern compatible with biotinidase deficiency which was subsequently confirmed.

Case 6

This boy was born at 36 weeks gestation by cesarean section with intrauterine growth retardation (birthweight 1750 g) due to the presence of severe preeclampsia and placental insufficiency in the mother. The parents were nonconsanguineous. The first pregnancy had resulted in a spontaneous abortion.

The patient was transferred to the neonatal intensive care unit and experienced hypoglycemia in the first few days of life (blood glucose 20-40 mg / dl). Glucose infusions at a rate of 4-6 mg / min were given. On the third day of life, he became more hypotonic and developed sclerema. Sepsis was suspected, and antibiotic treatment along with immunoglobulin infusions were instituted. On the eighth hospital day, acidotic respiration was noted. Blood pH was 7.32 and bicarbonate 14.1 mmol / L. Serum lactate and pyruvate concentrations were found to be slightly increased (28.1 and 1.0 mg / dl, respectively). Blood ammonia was 180 µg / dl, and paper chromatography of serum and urine samples was found to be normal. An EEG showed the presence of paroxysmal activity in the right hemisphere and a generalized burst suppression pattern. He died on the 13th day of hospitalization.

GC-MS analysis of the urine sample collected just before his death disclosed a pattern seen in biotin-dependent disorders. Serum biotinidase activity was subsequently measured and found to be absent.

Case 7

A 5.5-month-old male infant was first brought to our hospital because of developmental delay. He was the first child of a nonconsanguineous couple. He was seen at our hospital for the second time at the age of 12 months.

On examination, his skin was normal and he had sparse hair growth. He was profoundly hypotonic and unable to hold up his head, sit unaided or walk.

An MRI of the brain demonstrated cerebral cortical atrophy associated with demyelination of the cerebral white matter in the occipital lobes. Blood pH was 7.30 and bicarbonate 13.2 mmol / L. Blood ammonia was slightly increased (140 µg / dl). Serum lactate (45.8 mg / dl) and pyruvate (1.3 mg / dl) concentrations were moderately increased. The urinary organic acid profile was typical for a

biotin-dependent disorder. Serum biotinidase activity was measured and found to be normal.

Biotin (20 mg / day) therapy was initiated and the dose increased to 40 mg/day. The patient began to make developmental progress and, when last seen at three years of age, his development was appropriate.

Case 8

A 3.5-month-old female infant was referred to our hospital for evaluation of hypotonia, noisy respiration and difficulty in swallowing with the suspected diagnosis of Werdnig-Hoffman disease following a hospitalization period of 15 days and having been fed by nasogastric tube at another institution. She had been doing well during the first three months of life, but then began to have feeding and swallowing difficulties. Her parents were nonconsanguineous and had three other healthy children.

On examination, the patient was extremely hypotonic and was unable to hold up her head. Organic pathology of the larynx and nasopharynx was excluded by direct endoscopic examination.

Laboratory investigations revealed a blood pH of 7.31 and bicarbonate 12 mmol / L. A slight increase in serum lactate concentration was detected (32 mg / dl). Serum pyruvate concentration was normal (0.78 mg / dl) as were serum and urine amino acid concentrations and magnetic resonance imaging of the brain. Blood ammonia was slightly increased (152 µg / dl). GC-MS analysis of the urine sample was found to be compatible with a biotin-dependent disorder. Biotinidase activity in serum was normal.

On the grounds of these clinical and laboratory findings, one of the congenital lactic acidoses, particularly Leigh's encephalomyelopathy, was considered. Typical urinary organic acid profile and normal serum biotinidase activity led us to the diagnosis of holocarboxylase synthetase deficiency, and biotin at a dose of 20 mg / day was initiated. The dose of biotin was increased to 40 mg / day. The patient showed clinical improvement, began to tolerate oral feeding and became more active within 20 days. She was discharged from the hospital in good clinical condition but did not return to our unit for follow-up visits.

Discussion

There are two genetically determined biotin-dependent disorders. The first is HCS deficiency, the second a deficiency of biotinidase. These two conditions share some signs and symptoms. Patients with a deficiency of HCS present during the neonatal period with a life-threatening illness, whereas biotinidase

deficiency usually presents after three months of age[1-7]. The age of onset in HCS deficiency varies from one day to eight months[8]. In accordance with those reported in the literature, our patients with HCS deficiency had presented at 5.5 and 3.5 months. The age of the patients with biotinidase deficiency at the time of diagnosis ranged from the first few days of life to 30 months. Since the clinical course was complicated by sepsis in the case diagnosed within the first week of life (Case 6), it is difficult to say to what extent the metabolic defect had played a role in the development of clinical manifestations, although Collins et al.[9] reported a case that was symptomatic from birth. Contrary to the common belief that biotinidase deficiency usually presents later in the first year of life, two patients in our series (Cases 3 and 4) became symptomatic at 70 and 91 days of life, respectively[1-9].

Most children affected by a biotin-dependent disorder exhibit hypotonia, seizures and alopecia[1-12]. Of the six patients with biotinidase deficiency, four were hypotonic as were the two patients with HCS deficiency. Seizure was the initial symptom to bring two biotinidase-deficient patients (Cases 3 and 4) to our attention. The seizures are typically infantile, myoclonic or generalized, and usually do not respond to anticonvulsant therapy, as in the two patients presented[1-12]. Hair was sparse in all patients with biotinidase deficiency, except for the case detected in the newborn period, and in one of the patients with HCS deficiency.

Keratoconjunctivitis and optic atrophy may be noted in biotin-dependent disorders[1-12]. Keratoconjunctivitis was present in two patients (Cases 3 and 5) in our series. Affected children commonly exhibit skin rash in the form of eczema or seborrhea or severe desquamating lesions[1-12]. Such lesions were present in half of our cases with biotinidase deficiency. Patients may have respiratory problems such as apnea, stridor and hyperventilation[1-4,13]. In our series, Case 1 had laryngeal stridor as the initial symptom of the disease, and another (Case 2) had respiratory problems complicated by apnea.

As the children grow older and remain untreated, they will experience loss of vision and hearing of neurosensory type as demonstrated by VEP and BAEP studies[1-12]. Both of these studies were found to be abnormal in two of our patients (Cases 2 and 3) whereas one case (Case 1) had only VEP abnormalities and another (Case 4) only BAEP abnormalities. In the remaining half of the patients, VEP and BAEP studies could not be done. EEG abnormalities, including a burst suppression pattern, have been reported in patients with a biotin-dependent disorder[1-3]. Bioelectric abnormalities were detected on EEG tracings of all of our patients with biotinidase deficiency. The CT scan and MRI of the brain may show hypomyelination[1-3]. These two neuro-imaging studies were performed in

three patients. One CT (Case 5) and one MRI (Case 7) were interpreted as abnormal.

Patients with a biotin-dependent disorder may present with episodes of acidosis or with chronic compensated acidosis[1-3, 10-12]. Acidosis was present in all patients in our series as evidenced by low blood pH and bicarbonate. Both lactic and pyruvic acid are usually found to be elevated in serum and cerebrospinal fluid samples[1-3, 10-12]. A two- to seven-fold increase in serum lactate was present in our cases, whereas pyruvate was increased in all but two cases (Cases 6 and 8). Therefore, patients diagnosed as having primary lactic acidosis should always be evaluated by organic acid analysis to detect these conditions. A characteristic organic aciduria is seen in biotin-dependent disorders[1-3]. In addition to lactic aciduria, excretion of 3-methylcrotonyl glycine, 3-hydroxy-isovaleric acid, 3-hydroxypropionic acid and 2-methylcitric acid is indicative of a biotin-dependent disorder. GC-MS analysis of urine samples showed this typical organic acid pattern in five of our cases (Cases 3, 5, 6, 7 and 8) and prompted us to measure serum biotinidase activity, which was found to be absent in all six cases with biotinidase deficiency.

Hyperammonemia may be found during the acute metabolic episode, particularly in HCS-deficient patients[1-3]. Except for the newborn with biotinidase deficiency complicated with sepsis (Case 6), blood ammonia levels were within normal limits in our biotinidase-deficient patients. Two HCS-deficient patients, however, had slightly increased blood ammonia concentrations similar to what has been reported in the literature.

Amino acid chromatography was done in all patients. Half of the patients showed no abnormality in serum and urine amino acid patterns. Three patients (Cases 1, 2 and 3) had elevated serum and urine concentrations of alanine, and one patient (Case 4) had an increased urine alanine concentratilon. Alanine is known to be increased in conditions associated with lactate and pyruvate accumulation in serum, such as biotin-dependent disorders[14].

Children with these disorders may exhibit feeding problems[1-3]. Cases 3 and 8 in our series presented with swallowing difficulty necessitating nasogastric tube feeding in addition to hypotonia. Harmful effects of lactic acidosis on the nuclei of cranial nerves in the brainstem have been implicated in the pathogenesis of nasopharyngeal and laryngeal functional abnormalities[15].

The clinical picture of a biotin-dependent disorder may resemble that of many other diseases, such as acrodermatitis enteropathica, congenital lactic acidosis, intractable infantile seizures, intermittent maple syrup urine disease, seborrheic dermatitis, severe combined immune deficiency, Leigh's encephalomyelopathy

and Werdnig-Hoffman disease[2]. In our series, acrodermatitis enteropathica in Case 2, infantile spasms in Cases 3 and 4, congenital lactic acidosis and immune deficiency disease in Case 5, and Werdnig-Hoffman disease and Leigh's encephalomyelopathy in Case 8 were initially considered. To confirm the diagnosis, infections as well as true cardiorespiratory and gastrointestinal problems should be excluded, GC-MS analysis of the urine sample should be performed and biotinidase activity measured.

All symptomatic patients may respond well to pharmacologic doses of biotin[1-3,10-12]. We started with a daily total dose of 20 mg in two (Cases 1 and 2) and 10 mg in another two cases (Cases 3 and 4) with biotinidase deficiency. All patients displayed a dramatic response to the treatment, as evidenced by the disappearance of neurological and cutaneous symptoms and correction of metabolic acidosis. Only Case 2, who had a relatively long period of coma, developed gait disturbance, and Case 4 displayed BAEP abnormalities as sequelae of the disease. Biotinidase-deficient patients were doing well on a maintenance dose of 5 mg biotin / day. The response to 20 mg / day biotin treatment was partial in two HCS-deficient patients, and the dose of biotin was doubled subsequently as recommended in the literature[1-3, 10-12].

Biotin-dependent disorders affect both males and females, and consanguinity has been reported in 20 percent of cases[2]. There were five males and three females in our series, and of the eight affected cases, three (Cases 3, 4 and 5) were products of consanguineous marriages. The combined incidence of profound and partial deficiencies of biotinidase is 1 in 61,067 live births[2]. Detection of eight cases at a single metabolic unit during the last few years indicates that biotin-dependent disorders are not rare in our country, where the frequency of other metabolic disorders is also known to be high[16].

In conclusion, it can be said that biotinidase and HCS deficiencies share certain nonspecific signs and symptoms that suggest an infectious disease or cardiorespiratory and gastrointestinal problems. In countries such as Turkey where the frequency of metabolic diseases is high, both biotinidase and HCS deficiencies should be considered in children who experience infantile spasms, especially when they do not respond to anticonvulsive therapy, as well as in children with immunologic dysfunction, unexplained breathing abnormalities, skin rash and / or hair loss, regardless of the age of onset.

Thus, a high index of suspicion of a biotin-dependent disorder in such cases should lead to the measurement of urinary organic acids and serum biotinidase activity and to the initiation of biotin therapy before irreversible central nervous system damage occurs.

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