Familial infantile bilateral striatal necrosis
Clinical features and response to biotin treatment

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Abstract—Background: Infantile bilateral striatal necrosis (IBSN) encompasses several syndromes of bilateral symmetric spongy degeneration of the caudate nucleus, putamen, and globus pallidus. The familial form of IBSN is rare, and inheritance is either autosomal recessive or maternal. Method: The authors describe an Israeli Bedouin kindred in which 15 children born to consanguineous parents were affected with familial IBSN. They evaluated the clinical and radiologic evolution of the disease in 11 patients and the cerebral pathologic findings in one patient. Three of the children were treated with oral biotin 100 mg/day. Results: Inheritance was apparently autosomal recessive. The untreated children had a similar clinical picture including developmental arrest beginning at the age of 7 to 15 months, choreoathetosis, and dysphagia. Pendular nystagmus appeared at a late stage. MRI, performed at various stages of the disease, showed severe basal ganglia atrophy. Postmortem study in one patient showed severe atrophy of the lenticular nuclei with gliosis and loss of neurons. Biotin, 100 mg/day, administered to the proband over a period of 15 months, may have slowed progression. In two other children treatment was initiated earlier and appeared to arrest or improve disease. Conclusions: Familial infantile bilateral striatal necrosis was inherited as an autosomal recessive trait. Clinical features included developmental arrest, dysphagia, and choreoathetosis. Imaging and pathology showed atrophy and degeneration of the basal ganglia. Oral biotin may have benefited three children.

Infantile bilateral striatal necrosis (IBSN) is a rare neurologic disorder characterized by symmetric degeneration of the caudate nucleus, putamen, and occasionally the globus pallidus, with little or no involvement of the rest of the brain. The diagnosis was based on pathologic findings until the advent of CT and MRI. Clinical features include developmental regression, choreoathetosis, dystonia, spasticity, dysphagia, failure to thrive, nystagmus, optic atrophy, and mental retardation. Prognosis is usually poor with spastic quadriplegia followed by death usually due to intercurrent infection. The differential diagnosis of basal ganglia degeneration in childhood includes acute disseminated encephalomyelitis, carbon monoxide intoxication, methanol intoxication, anoxic-ischemic encephalopathy, small vessel arteritis, symmetric arteriovenous destructive malformations, juvenile Huntington chorea, Hallervorden–Spatz syndrome, status marmoratus, Wilson disease, guanidinoacetate methyltransferase deficiency, Leigh encephalopathy, and IBSN. Meningitis, encephalitis, subacute sclerosing panencephalitis, Creutzfeldt–Jakob disease, hemolytic-uremic syndrome, and neuroacanthocytosis are known causes of bilateral striatal lesions in childhood. Basal ganglia degeneration may also be manifested by basal ganglia calcification due to prenatally or postnally acquired hypoxic-ischemic, infectious, and toxic insults, dystrophic calcification, or calcium metabolism abnormalities, such as hypoparathyroidism, pseudohypoparathyroidism, and pseudopseudohypoparathyroidism. The latter group of disorders is often erroneously classified as Fahr syndrome. Patients with these abnormalities often have severe encephalopathies. Metabolic diseases associated with basal ganglia calcification include Cockayne syndrome; mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like syndrome (MELAS); and Kearns–Sayre syndrome.

Familial IBSN has been reported in rare cases in
England, France, Japan, and the United States. The known genetics include mitochondrial inheritance (MELAS, Leigh disease) and mutations of the adenosine triphosphatase 6 gene (complex V). Autosomal recessive pattern was suggested in several reports because in all cases, the parents were healthy and the affected children were of both sexes.

We report on an Israeli Bedouin kindred with familial IBSN with an apparently autosomal recessive mode of inheritance. The clinical manifestations, radiologic evolution, and neuropathologic characteristics of the disease are described, as is the response of three patients who were treated with biotin on the basis of a report on its successful use in another basal ganglia disease.

**Patients and methods.** We studied 11 children with IBSN over a 15-year period; four others were known to be affected (figure 1). All were members of six interrelated families belonging to a single Hammula (clan) or kindred (see figure 1). The members of the sixth family did not know the exact link to the kindred but they bore the same family name. The founder migrated from Egypt to Israel over 300 years ago. In five families, the parents are first-degree cousins, and in the sixth, they are second-degree cousins. The table summarizes the clinical characteristics of the 11 patients.

**Clinical findings.** Age at onset of the disease ranged from 7 to 15 months. Reason for referral was sudden appearance of dysphagia and vomiting, failure to achieve developmental milestones, or the onset of motor and cognitive regression. On physical examination, the children appeared alert and in a responsive nonverbal state. The medical files revealed a head circumference at birth below the second percentile, measuring 31 to 33.5 cm (mean 32 cm). Growth charts showed a steep decline in the weight curve at the start of the symptoms; all patients fulfilled the criteria for failure to thrive. At presentation, all children had achieved a developmental age of 5 to 6 months; four were able to walk with assistance and five spoke a few words (developmental age of 12 to 15 months). All children were referred for neurologic evaluation during the first 15 months of life.

The most prominent neurologic finding was choreoathetoid movements of the face, trunk, and extremities. Gag reflex was normal, supporting the diagnosis of pseudobulbar palsy.

Over the next few years, the untreated children became bedridden and were unable to perform voluntary movements. The choreoathetosis progressed to hemiballismus combined with dystonic postures. Acquired horizontal pendular nystagmus, commonly occurring in congenital and acquired disorders of myelin, appeared in Patient VI-14 at age 3.5 years and Patient VI-9 at age 5 years; optic atrophy later appeared in these two patients (age 10 and 9). One patient experienced seizures. All patients who reached age 4 years and were not treated developed spastic quadriplegia with scissoring of the legs, spasticity, hyperreactive tendon reflexes, and a negative Babinski reflex. At age 9, 11, and 6 years, Patients VI-9, VI-14, and VII-10 were able to hear, fixate, and follow eye movements and to produce a social smile when they saw their parents.

**Representative case (Patient VI-14).** The patient was born after an uneventful pregnancy and delivery at 37 weeks of gestation. Her development was normal until age 15 months, when she was brought in for evaluation because of an inability to walk alone. Examination revealed truncal hypotonicity, but the tendon reflexes were brisk (3+). She could sit without support, crawl on all fours, and pull herself up from a sitting position to a standing position.

Reevaluation was done at 21 months. The mother reported that during the 6 months prior to the visit, the child had lost the ability to crawl. She was no longer able to do purposeful hand movements or to speak. There were signs of increasing difficulty in swallowing and weight loss. On examination, the most prominent neurologic feature was choreoathetosis of the trunk, face, and limbs. The child could not stand, and ambulated by shuffling on her buttocks; this explained the pressure sores noted on the lateral malleoli. When she was pulled from a supine to a
sitting position, she showed extreme head lag. When helped to stand, she arched her head backwards in an opisthotonic posture. She could reach for an object, but her grasp was clumsy.

Ten months later, gastrostomy feeding was initiated because of dysphagia and severe weight loss. At the age of 40 months, pendular nystagmus was first noted, with no external ophtalmoplegia or oculomotor dyspraxia. The fundi were normal.

On the last examination at 120 months, there were choreoathetoid and hemiballistic movements of the extremities with spastic quadriplegia. Although the child was bedridden and had no verbal skills, she was able to communicate nonverbally with her parents and caregivers. Sensation was normal. Optic disc examination revealed normal range.

Muscle specimens were taken to assess mitochondrial respiratory chain enzyme activity. All results were within normal range.

Owing to the apparent autosomal recessive inheritance of the disease in our patients, which distinguishes them from patients with mitochondrial ATPase 6 point mutations, which has a maternal inheritance,13,14 we are currently performing a genome-wide search in our families, to determine chromosomal linkage of the IBSN gene.

The following neurophysiologic studies were done: EEG, visual evoked potentials, brainstem auditory response, EMG, nerve conduction studies, and somatosensory evoked potentials. Again, all results were normal or negative. However, in Patient VI-14, at age 11 years, brainstem auditory response showed clear evidence of aberrant conduction on both sides, and visual evoked potentials showed slowing of cortical transmission on ocular stimulation.

Radiologic studies. CT was performed initially in Patient VI-14 at age 15 months and findings were compatible with brain atrophy. MRI was performed in Patients VI-2 (age 16 months), VI-9 (age 6 and 9 years), VI-12 (21 months), VI-14 (15 months, 6 years, 11 years), VI-20 (11 months), VII-5 (1 year), and VII-10 (20 months, 6 years). MRS was performed in the proband, Patient VI-12, at 21 months and was normal.

The radiologic evaluation was based on a composite taken from multiple individuals with IBSN. MRI findings identified a four-stage radiologic evolution. Initial MRI scans, performed at 11, 12, and 15 months, revealed no abnormalities (figure 2A). Thereafter, at 20 and 21 months, they showed caudate nuclei and putamen of normal size, but on T2-weighted images, bilateral, symmetric, hyperintense signals were visible in the putamina (see figure 2B). Follow-up at 6 years revealed further changes. The caudate nucleus and the putamen were atrophic, and the putamen showed a low signal on T1-weighted images.

**Table Clinical and radiographic findings of the patients**

| Patient no. | VI-2 | VI-6 | VI-9 | VI-12 | VI-14 | VI-20 | VII-3 | VII-4 | VII-5 | VII-10 | VII-11 |
|-------------|------|------|------|-------|-------|-------|-------|-------|-------|--------|--------|
| Findings    |      |      |      |       |       |       |       |       |       |        |        |
| Present age, y | 1½2  | Age at death 4½ | 9    | 2     | Age at death 11 | 1½2  | Age at death 2 | Age at death 1½2 | Age at death 6 | Age at death 4 |
| Onset of neurologic deterioration, mo | 9    | 7.5  | 7    | 12    | 15    | 10    | 14    | 7     | 9     | 12     | 12     |
| Vomiting + gastrostomy feeding | –    | +    | +    | +     | +     | –     | +     | +     | +     | –      | +      |
| Neurologic findings |      |      |      |       |       |       |       |       |       |        |        |
| Axial hypotonia | +    | +    | +    | +     | +     | +     | +     | +     | +     | +      | +      |
| Limb hypertonia | –    | +    | +    | +     | +     | +     | +     | +     | +     | +      | +      |
| Hyperactive deep tendon reflexes | –    | +    | +    | +     | +     | +     | +     | +     | +     | +      | +      |
| Choreoathetosis | +    | +    | +    | +     | +     | –     | +     | +     | +     | +      | +      |
| Pendular nystagmus | –    | –    | +    | –     | +     | –     | –     | –     | –     | –      | –      |
| Quadriplegia | –    | –    | –    | +     | –     | +     | –     | –     | +     | –      | +      |
| Optic atrophy | –    | NE   | +    | –     | +     | –     | –     | –     | –     | –      | NE     |
| Pathologic MRI change | +    | NE   | +    | –     | –     | –     | –     | –     | +     | –      | –      |

NE = not examined.
and a high signal on T2-weighted images, compatible with malacia of the deep gray matter. In addition, the ventricles had enlarged ex vacuo (see figure 2C). In the fourth stage, at age 10 and 11 years, MRI scans showed a small, residual caudate nucleus and putamen with abnormal signals, like in the previous examination. Diffuse parenchymal loss was evident, and corpus callosum had thinned (see figure 2D). There were no signs of involvement of the brainstem, periaqueductal gray matter, centrum semiovale, cerebral peduncles, or cerebellar hemispheres—lesions that are typical of Leigh disease.13

Pathologic findings. An autopsy was performed on Patient IV-14. The brain weighed only 850 grams (normal range: 1,143 to 1,318 grams). The whole brain was fixed in 10% buffered formalin, cerebral hemispheres were sectioned in the coronal plane, and brainstem and cerebellum were cut in the horizontal plane. Representative samples from the various regions were postfixed in 10% buffered formalin, embedded in paraffin, and stained with hematoxylin and eosin, Luxol fast blue for myelin, and Bielschowsky stain for axons. Coronal sections of the cerebral hemispheres revealed marked hydrocephalus ex vacuo, most prominent in the lateral ventricles (figure 3, A and B). There was severe atrophy of the lenticular nuclei, with retention of their normal color. The characteristic bulge of the caudate nucleus into the anterior part of the lateral ventricle was absent (see figure 3A). The cerebellum and brainstem were grossly unremarkable, except for the presence of a pale substantia nigra.

Microscopic examination showed prominent gliosis and severe loss of neurons throughout the caudate, putamen, globus pallidus, and claustrum (see figure 3C). The changes were somewhat less pronounced in the globus pallidus, which exhibited a larger number of preserved neurons than the caudate and putamen. Gliosis and loss of neurons were also noted in the substantia nigra. The thalamus, mammillary bodies, hypothalamus, locus ceruleus, and cerebellum were normal. The cerebral cortex was normal, without appreciable neuronal loss.

Treatment. Oral treatment with biotin (Mercury Co.) 100 mg/day was given to three patients with the approval of our institution’s Ethics Committee. The proband (VI-12) began treatment at age 16 months. During the 6-month follow-up, the disease did not progress, and mild improvement was noted in gross and fine motor capabilities. The head lag, prominent before initiation of treatment, disappeared, indicating better truncal tone; the child was able to pull himself up in his trolley from a recumbent to a sitting position and to grasp a familiar toy, maneuvers he could not perform before treatment. He reached for distant objects by crawling and rolling over. However, during an additional 9 months of follow-up, there was no further progress.

Patient VI-2 was also 16 months old when treatment with biotin 100 mg/day was initiated. Over a 4-month period, he did not regress motorically and the chorea diminished. Gastrostomy feeding was unnecessary and he began to understand a few words.

Patient VI-20 received biotin starting at 10 months. During 4 months of follow-up, he achieved the ability to sit, crawl, walk with support, hold his bottle, and understand a few words. He did not need gastrostomy feeding.

Discussion. IBSN is a rare syndrome encompassing several clinicopathologic entities that share a common final pathway; namely, bilateral symmetric spongy degeneration of the caudate nucleus, putamen, and occasionally the globus pallidus. It was first described in 19245 and named IBSN in 1974.1 The early cases,1 as well as those described more recently, were clinically heterogeneous. Age at onset varied from infancy to adulthood, and some patients presented with a progressive disorder whereas others had an acute or subacute neurologic anomaly, occasionally preceded by an acute febrile illness. MRI evaluation used in later cases showed the characteristic involvement of the corpus striatum and evolution of the disease. Several reports8,17,18 suggested a classification of the syndrome by age at onset, clinical evolution, and familial or sporadic occurrences. On this basis, the reported cases can be divided into three subgroups: 1) definite or probable subacute necrotizing encephalomyelopathy (Leigh
disease); 2) familial degeneration of the striatum with insidious onset and slow, progressive course; and 3) abrupt neurologic dysfunction following an acute systemic illness. Our patient had the second type, which has an autosomal recessive mode of inheritance and, in contrast to the acute form, a grave prognosis, with death in the first or second decade.

There are several reports in the literature on familial IBSN of early onset (<3 years). The patients in our series, which is the largest reported so far, had similar initial clinical manifestations—i.e., developmental arrest and in some cases regression of motor and cognitive skills similar to the earlier cases—but there were differences in the extrapyramidal and ocular manifestations. In our patients, extrapyramidal involvement was manifested as choreoathetosis, whereas in the previous reports, the disease most often was associated with a movement disorder: either titubation, ataxia, and dystonia, or choreoathetosis, combined with a progressive decline in mental and motor performance, as well as dysphagia. The ocular involvement, which appeared at a late stage, consisted of pendular nystagmus and optic atrophy, whereas in the other reports it included esotropia, nystagmus, optic atrophy, or blindness. Some patients also had seizures. In all the cases, including our own, neuropathologic study showed necrosis and loss of neurons in the caudate and putamen.

A variety of toxic, metabolic, and degenerative conditions may affect the basal ganglia in children. MRI findings of hyperintensity of the striatum on T2-weighted images narrows the differential diagnosis to a few entities such as Leigh disease, juvenile Huntington disease, MELAS, hypoxic ischemic injury or hypoglycemic injury, and IBSN. Mutations of the adenosine triphosphatase 6 gene (complex V) are a subgroup of Leigh disease with maternal inheritance. Although they have been classified as bilateral striatal necrosis, they differ from the IBSN in our patients, wherein inheritance was apparently autosomal recessive. Our cases are further distinguished by later age at onset, lesser severity of symptoms, normal levels of lactate and pyruvate, and normal morphology on electron microscopy muscle biopsy studies.

The treatment of three of our patients with biotin was prompted by the report of a novel basal ganglia disease characterized by subacute encephalopathy, confusion, and dysarthria and dysphagia progressing to severe cogwheel rigidity, dystonia, and quadriparesis. The symptoms disappeared within a few days following treatment with biotin 5 to 10 mg/kg/day, leaving no neurologic sequelae. In our series, we treated the proband (VI-12) with 100 mg/day (10.0 mg/kg) for 6 months. During that period, we had the impression that the disease ceased to progress, and there was even some reversal in the neurologic symptoms. However, further follow-up to 15 months failed to yield any additional improvement. In Patients VI-2 and VI-20, biotin treatment was initiated at an earlier stage of the disease, and it seemed to
have beneficial influence on its progression. The patients retained the motor milestones already achieved, and their cognitive capabilities apparently progressed. The chorea decreased, and the need for gastrostomy feeding was avoided.

Biotin is a water-soluble B-complex vitamin found in egg yolk, yeast, and liver. In humans, biotin serves as a prosthetic group in four carboxylase enzymes that are directly involved in gluconeogenesis, fatty acid synthesis, and amino acid catabolism. Three of the enzymes—pyruvate carboxylase, propionyl-CoA carboxylase, and β-methylcrotonyl-CoA carboxylase—are mitochondrial; the fourth, acetyl CoA carboxylase, is cytosolic. Pyruvate carboxylase catalyzes the conversion of pyruvate to oxaloacetate, an intermediate in the biosynthesis of phosphoenolpyruvate and ultimately glucose. Acetyl CoA carboxylase catalyzes the formation of malonyl CoA from acetyl CoA, the first committed step in the biosynthesis of fatty acids. Propionyl CoA carboxylase is involved in the catabolism of several branched-chain amino acids and fatty acids of odd-carbon chain lengths by converting propionyl CoA to methylmalonyl CoA, which ultimately enters the tricarboxylic acid cycle. β-methylcrotonyl CoA carboxylase is involved in leucine catabolism by the conversion of β-methylcrotonyl CoA to β-methylglutaconyl CoA. Deficiencies of the carboxylases lead to abnormally high concentrations of metabolic intermediates, which can have profound effects on other pathways.

Biotin has been found to be effective in the treatment of multiple carboxylase deficiency disorder, characterized by subnormal activity of all three biotin-dependent mitochondrial carboxylases in peripheral blood leukocytes and skin fibroblasts, as well as deficient activity of acetyl CoA carboxylase in fibroblasts. The disorder has been attributed to a defect in holocarboxylase synthetase. Most affected patients become symptomatic soon after birth, compared to patients with biotinidase deficiency, who usually exhibit clinical manifestations after 3 months of age. Nevertheless, there is an overlap in the ranges of age at onset.

Biotin deficiency in humans almost never occurs spontaneously. Overt clinical symptoms include alopecia and cutaneous abnormalities such as dermatitis, erythematous periorificial rash, dryness, and fungal infection. Neurologic symptoms, noted in infants, erythematous periorificial rash, dryness, and spontaneous. Overt clinical symptoms include alopecia, erythematous periorificial rash, dryness, and spontaneous. Overt clinical symptoms include alopecia, erythematous periorificial rash, dryness, and spontaneous.

The consumption of raw eggs, which contain avidin, has led to biotin deficiency in several children and adults. Biotin deficiency may also occur in patients receiving long-term parenteral nutrition without biotin, and following prolonged use of the anticonvulsants phenytoin, primidone, and carbamazepine.

The putative mechanism underlying the action of biotin in preventing deterioration in IBSN is currently unknown. In rat brain, biotin is transported through cerebral capillaries by a low-affinity saturable process that depends on the presence of the free carboxylic acid group of the biotin side chain. The choroid plexus appears not to be involved. Normal biotinidase values in IBSN suggest that the disease might be caused by a defect in the biotin transporter system across cerebral capillaries. We hypothesize that the high doses of biotin used for treatment in our patients might have assured some biotin transport into the brain, thereby affecting the clinical course.

Acknowledgment
The authors thank the patients and their parents for their compliance with the medical examinations and treatment.

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