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Biotin-responsive basal ganglia disease: a novel entity

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Summary

We describe a novel, biotin-responsive basal ganglia disease in 10 patients. At onset, it appears as a subacute encephalopathy, with confusion, dysarthria and dysphagia with occasional supranuclear facial nerve palsy or external ophthalmoplegia, and progresses to severe cogwheel rigidity, dystonia and quadriparesis. These symptoms disappear within a few days if biotin (5–10 mg/kg/day) is administered, and there are no neurological sequelae. They reappear within 1 month if biotin is discontinued. Patients diagnosed late, or who have had repeated episodes, suffer from residual symptoms such as paraparesis, mild mental retardation or dystonia. The numerous biochemical studies of intermediary metabolism, like the autoimmune and toxicological studies, enzyme assays including biotinidase, carboxylase and lysosomal activities, and bacterial and viral studies were all normal. The aetiology may be related to a defect in the transporter of biotin across the blood–brain barrier. The only consistent radiological abnormality was central necrosis of the head of the caudate bilaterally and complete, or partial, involvement of the putamen on brain MRI. This was present during the initial acute encephalopathy and remained unchanged during follow-up of 3–10 years. Although its aetiology is unknown, it is important to recognize this disease, since its symptoms may be reversed and the progression of its clinical course prevented simply by providing biotin.

Keywords: biotin; basal ganglia disease; dystonia

Abbreviations: carbidopa = L-α-hydrazino-3,4-dihydroxy-α-methylhydro-3-phenylpropenoic acid monohydrate; CoA = coenzyme A; L-dopa = L-3,4-dihydroxyphenylalanine; PCR = polymerase chain reaction

Introduction

Bilateral striatal lesions have emerged as a novel neuroradiological syndrome after the introduction of brain MRI and CT, in investigations of patients with extrapyramidal tract signs (Leuzzi *et al*., 1988). Extrapyramidal tract disorders, particularly dystonia, are common in childhood (Segawa, 1993). Some of these occur without defined aetiologies, and others as a part of a defined disease in the CNS (Segawa, 1993). Most cases with bilateral striatal lesions are of acute onset (Roig *et al*., 1993). Common causes range from hypoxia to CNS infections (Aicardi *et al*., 1985; Burstein and Breningstall, 1986; Donovan and Lenn, 1989; Kappelle *et al*., 1989), mitochondrial encephalopathies (Pavlakis *et al*., 1984; Nigro *et al*., 1990), or autoimmune causes (Devilat *et al*., 1993). Certain inborn errors of metabolism are associated with discrete degeneration in parts of basal ganglia, e.g. glutaric acidemia type 1 (Brismar and Ozand, 1995), methylmalonic acidemia (Korf *et al*., 1986) and 3-methyl-glutaconic aciduria (Brismar and Ozand, 1994). Despite extensive investigations, the aetiology remains unclear in a large number of cases (Erdohazi and Marshall, 1979; Mito *et al*., 1986). However, an L-dopa (L-3,4-dihydroxyphenyl-alanine)-responsive form of dystonia (Nygaard *et al*., 1991), idiopathic torsion dystonia (Marsden and Harrison, 1974), childhood onset parkinsonism (Narabayashi *et al*., 1986) and acute benign infantile bilateral striatal necrosis have been described in detail (Roig *et al*., 1990).

Over 60 patients with clinical and neuroradiological evidence of basal ganglia disease have been followed up in

our service during the past 12 years. A unique group of 10 patients among them have presented with acute symptoms of a basal ganglia disease, which appears to be a familial disease with possible autosomal recessive inheritance, and which responds within days to large doses of biotin. This biotin-responsive basal ganglia disease is associated with destruction of caudate heads centrally and partial or complete loss of the putamen. We describe in detail the clinical and neuroradiological features of these 10 cases and compare them with those of other basal ganglia diseases of childhood.

Case presentations

Patients 1 and 2

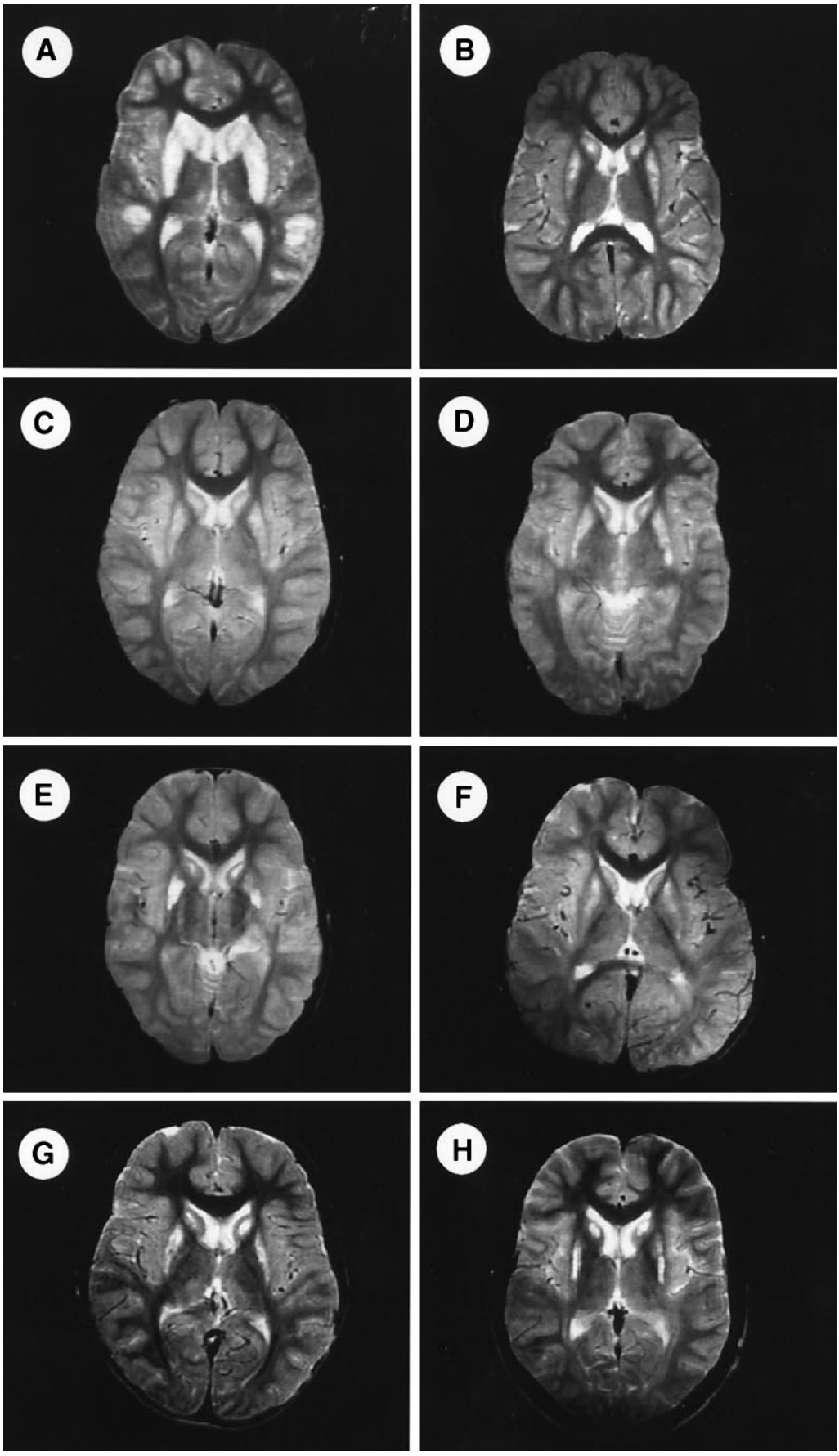
Patient 1 (Sa. Al S.)

This was the first patient we encountered 10 years ago, when she was 5 years old. Three weeks before referral, she developed a mild upper respiratory tract infection, mild fever and vomiting for 1 week. She then gradually developed stiffness of her extremities, lost all motor function, and presented with generalized tonic–clonic, later clonic, seizures. She was treated with diazepam, cogentin, epanutin and acyclovir at the referring hospital. She became deeply comatose and was referred to us with a diagnosis of encephalitis. The parents were first cousins. Four siblings, two boys and two girls, each died of a similar disease without diagnosis (at 1, 3, 4 and 5 years of age, respectively). There are four normal siblings and another sister (Patient 2) who has the same disease. On admission, Patient 1 was comatose. She had no visual pursuit. She was rigid more on left side than right; and was less stiff while asleep. She was quadriparetic with Babinski's sign bilaterally, with deep tendon reflexes (3+ in upper and 4+ in lower extremities), and sustained bilateral ankle clonus. Blood and CSF chemistry, and bacteriological studies were normal (see details in the Results section); blood and CSF titres for measles, mumps, herpes, Epstein–Barr virus and enteroviruses, and polymerase chain reaction (PCR) studies for herpes were all negative. While she was in a coma, her EEG revealed generalized slowing and asymmetrical sleep spindles in the left hemisphere. The brain CT from the referring hospital showed dilated ventricles and scattered white matter disease. The brain MRI on admission indicated central necrosis of the caudate heads and necrosis in the putamen (not shown). She showed slight improvement and was discharged back to the referring hospital. She was placed on L-dopa (100 mg twice daily for 2 weeks), and then on thiamine, carnitine, phenobarbital and diazepam, with no improvement. Three months after discharge, biotin was added at 5 mg/kg/day. She immediately showed improvement, initially walking clumsily and 6 months later independently, with an unsteady gait. Speech reappeared within 1 month. Mild left hemiparesis remained, with no rigidity or dystonia. Deep tendon reflexes became normal. Neurophysiological tests, including a repeat EEG, were normal (see details in the Results section). During the next 3 years she returned totally to normal and started to attend grade school where she was a below average student. A WISC-R (Wechsler Intelligence Scale for Children—Revised), standardized for the Saudi language and culture, indicated an IQ of 95, with mild attention deficit disorder. One year from discharge all medications other than biotin were discontinued.

Her father decided that she was completely cured and discontinued biotin when she was 8 years old. Within 1 month she developed grand mal seizures, rigidity and dystonia. She arrived at the emergency room in a coma and with an oculogyric crisis, with her tongue protruding, her back arched, severe chorea of the mouth, facial dystonia and severe intermittent dystonia of her extremities and tetraplegia. Deep tendon reflexes were 4+ in the upper and lower extremities, with Babinski's sign bilaterally, and sustained bilateral ankle clonus. Biotin was reinstated. The oculogyric crisis resolved within 24 h. She regained consciousness, started to talk, and the dystonia disappeared. In 2 days, the rigidity of the lower extremities lessened but did not disappear and she remained paraparetic. She started to ambulate in a wheelchair. An EEG was normal but the brain MRI showed severe oedema and increased destruction of caudate heads and putamen with scattered central white matter disease (Fig. 1A). Other neurophysiological studies, and blood and CSF chemistry were normal (see details in the Results section).

She has never become totally normal again, although during the following 7 years the parents have been very compliant. She did not experience another acute crisis, but has severe motor handicap with bilateral supranuclear facial palsy, increased deep tendon reflexes and contractures at the ankles. She has severely slurred speech. A repeat psychometric evaluation at the age of 10 years indicated an IQ of 75. She is attending a handicapped school facility at the age of 15 years. Her present appearance together with her affected sister (Patient 2) is shown in Fig. 2.

Fig. 1 A–H Brain MRIs of Patients 1–8, respectively. All show bilateral symmetrically increased T_2-signal intensity within the central parts of caudate nuclei and in parts, or all, of putamen. The MRI for Patient 1 (**A**) was obtained at the age of 9 years, at the time of a second oculogyric crisis. Her brain MRI 3 months before the episode showed a similar appearance to the brain MRIs of Patients 2–8. The heads of caudate and putamen were swollen due to acute oedema, which also involved the anterior limb of the internal capsule. There was increased T_2-signal intensity at several locations in the grey–white matter junction, particularly prominent at posterior parietal region. The MRI for Patient 2 (**B**) was obtained at the age of 3 years, when she experienced a mild episode of dystonia. The MRI for Patient 3 (**C**) was obtained at the age of 14 years, 7 years after the first crisis. The MRI for Patient 4 (**D**) was obtained at the age of 14 years, 5 years after the first crisis. The MRI for Patient 5 (**E**) was obtained at the age of 8 years, 3 years after first crisis. The MRI for Patient 6 (**F**) was obtained at the age of 7 years, 6 years after the initial crisis. The MRI for Patient 7 (**G**) was obtained at the age of 6 years, at the time of initial crisis. The MRI for Patient 8 (**H**) was obtained at the age of 14 years, at the time of initial crisis.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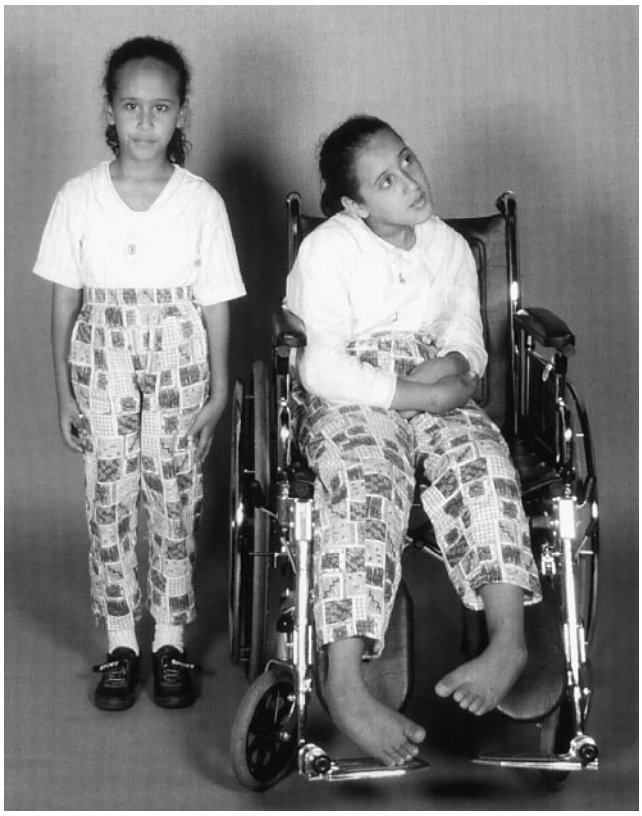

Fig. 2 Patient 1 (in the wheelchair) and her sister, Patient 2, who had no neurological signs (standing).

Patient 2 (Am. Al S.)

This patient (sister of Patient 1) was first seen at the age of 3 years, since the parents were now concerned about the disease and aware of its consequences if untreated. Her father had recently noticed intermittent dystonia of her hands a few weeks before arrival. On physical examination, there was no gait abnormality and no choreoathetosis, but there was a possible periodic dystonia of the left hand. Deep tendon reflexes were normal with no pathological reflexes present. Fundoscopic examination was normal. The blood and CSF chemistry, chromosome studies and neurophysiological studies were within normal limits (see details in the Results section). Despite the unimpressive clinical presentation, a brain MRI was obtained which showed severe degeneration of the central part of caudate heads and the putamen (Fig. 1B). She was immediately placed on biotin, 5 mg/kg/day. During the next 6 years she remained asymptomatic with no acute episode of the disease. She is now 9 years old, attending grade school where she is an average student.

Patients 3 and 4

Patient 3 (Az. Al Sh.)

This patient is at present 15 years old. She was referred, 8 years ago, with a presumed diagnosis of brainstem encephalitis. Three months before admission she presented with confusion, failing to recognize her parents and siblings. Three weeks prior to admission she complained of frontal headache, continuous vomiting and lethargy. She stopped walking and talking, and was unable swallow. Family history revealed that her distantly related parents have two normal boys and one normal girl; another sister died at the age of 16 years, following similar complaints. Patient 4 is another brother of hers. The parents are middle class and well educated. There was no history of exposure to a toxic substance. At the time of admission, systemic examination was normal. Neurologically Patient 3 was drooling, did not talk or respond to verbal comments, had severe rigidity in the upper and lower extremities, and lay in an opisthotonic posture. The deep tendon reflexes were 4+ out of 5, with sustained bilateral ankle clonus. Her right hand showed cortical fisting with a flexed right arm; her arms, hands and feet showed dystonic posturing. Fundoscopic examination was normal. A large number of blood, urine, CSF and fibroblast investigations were normal (see details in the Results section). She was given biotin (5 mg/kg/day) and started to improve dramatically within 24 h, walking talking and swallowing. She went home as a normal child within 3 days. She has been followed up in the clinic on a 3–6 monthly basis. On two occasions, she discontinued biotin inadvertently and on both occasions she became confused after 1 month, with dystonia of the hands. On one of these occasions L-dopa with carbidopa [L-α-hydrazino-3,4-dihydroxy-α-methylhydro-3-phenylpropenoic acid monohydrate] at a dose of 100 and 25 mg/day was tried with no response. The recurrent symptoms, however, promptly disappeared upon starting biotin. Her brain MRI, obtained on a 2-yearly basis, remained unchanged compared with the initial one (Fig. 1A–C). At present she is an excellent student attending grade school, with normal neurological findings except for mild stuttering.

Patient 4

This patient has already been described (case 8 in Dabbagh *et al*., 1994). His brain MRI is shown here in Fig. 1D.

Patient 5 (M. Al H.)

This girl was first seen 6 years ago, when she was 5 years old. One month prior to referral she had generalized convulsions, which recurred 1 week later. She became tetraparetic, and lost her speech and comprehension. Her parents are second cousins; five siblings died with similar symptoms, after episodes of vomiting and diarrhoea. The father, who was also married to another second cousin, had a son from the second marriage, who died with progressive encephalopathy following vomiting and diarrhoea. The family is of low socio-economic class. No history of exposure to toxic substances could be elicited. At the time of the initial examination the patient lay in decorticate posturing. She was hypertensive and was placed on nifedipine (30 mg once daily). There were no other systemic findings except for the

neurological symptoms. Her tongue was sticking out and the neck was retroflexed. She showed tetraplegic rigidity of the upper and lower extremities. The deep tendon reflexes were increased, with Babinski's sign. She could not swallow and had to be fed by nasogastric tube. Ophthalmological examination showed a normal fundus. She had no seizures during her stay in the hospital. Blood and CSF chemistry, and EEG were normal (see details in the Results section). She was given biotin (5 mg/kg/day). Within 72 h, she started to walk and talk. Her hypertension was quickly controlled. Nifedipine was discontinued within 1 week. She was normal neurologically 1 month later except for slight dysphonia.

She has been followed up on a 3-monthly basis since then. Her psychometric evaluation and speech were normal 10 months later. At present she is 11 years old, attending grade school with an above average performance. She shows only mild attention deficit disorder and dysarthria. The parents never failed to give biotin and she has not had a repeat episode. Her initial brain MRI is shown in Fig. 1E, the lesions have remained unchanged at her in 2-yearly follow-ups, which have now continued for 6 years.

Patient 6 (S. Ba N.)

This boy was first seen at the age of 2 years, seven years ago. He had appeared normal until the age of 1 year, when he started to lose motor milestones: falling frequently, developing abnormal synkinesis of the left arm and hand, occasional dystonia of the right hand, and becoming tetraparetic by the time of referral. His speech was affected only minimally, with age-appropriate comprehension and speech content. The parents were first cousins. Later, they had a second son who developed Tourette's syndrome at the age of 4 years. Extensive studies of the second child, including brain MRI and glucose-PET, were normal. A maternal cousin was recently found to have biotin-responsive basal ganglia disease (case history not included). The neurological examination of Patient 6 at 2 years of age indicated mild rigidity of the upper and lower limbs, poor fine motor performance, normal deep tendon reflexes with no pathological reflexes. All chemical and neurophysiological studies were within normal limits (see details in the Results section). His brain MRI is shown in Fig. 1F. He has been on biotin (5 mg/kg/day) for 7 years now, and has had no acute episodes. His neurological symptoms disappeared within a few days. He is currently at grade school, an above average student and is excellent in sports. However, the father has noticed that when they fail to give biotin for a while, he becomes mildly confused with decreased school performance, which disappears after reinstating biotin.

Patient 7 (T. Al O.)

This boy was first seen 3 years ago when he was 6 years old. He had been well until 1 week before, when he developed sudden left hemiplegia without a precipitating cause. A brain CT obtained at the referring hospital revealed bilateral basal ganglia lesions. The physician was aware of the biotin-responsive basal ganglia disease, and he immediately referred the patient to us. The patient's parents are first cousins. Four siblings, who were diagnosed by us as having Sandhoff's disease, had died. There are four normal children. Two maternal cousins have mild mental retardation of unknown cause. The physical examination indicated a left hemiparetic child with dystonia of the left upper and lower extremities, with ptosis of the left eye, and mild left supranuclear facial paralysis with no impediment of upward gaze. The deep tendon reflexes on left side were exaggerated, with a Babinski sign on the left and a normal plantar reflex on the right side. His speech was slurred. Examination of the other cranial nerves was normal. Leucocytes were tested for hexosaminidase activity, which was normal. Homocystinuria is a common disease among the members of his tribe. Repeated urine and blood analysis failed to indicate cystathionine β-synthase deficiency. The other blood chemistry and neurophysiological investigations were normal (see details in the Results section). His brain MRI is shown in Fig. 1G. He was placed on biotin, and the symptoms disappeared promptly within 3 days. He showed only mildly slurred speech 2 weeks later, with no trace of left hemiplegia or related neurological findings. His psychometric evaluation indicated an IQ of 85. He is attending grade school with acceptable performance.

Patient 8 (A. Al K.)

The patient was hospitalized 3 years ago at the age of 14 years with an akinetic mute state. He had developed quadriparesis 10 months prior to referral with eventual mutism and loss of speech, swallowing and comprehension. The parents were first cousins and an older brother had developed acute encephalopathy following a non-specific febrile disease; he had remained without diagnosis despite extensive viral and bacteriological studies and had died 10 years before. On examination, he could not sit or walk; he had increased rigidity of the upper and lower limbs, poor co-ordination, no tremors and increased deep tendon reflexes with Babinski's sign bilaterally. Blood and CSF chemistry, and serology, as well as bacteriological and viral studies were normal (see details in the Results section). His EEG was abnormal with 2–3-Hz activity fronto-temporally, with left side preponderance. No reproducible cortical or peripheral potentials were recorded in somatosensory evoked potential studies. The brainstem auditory and visual evoked potentials were poorly reproducible. The brain MRI is shown in Fig. 1H. He was placed on biotin, but only responded partially, by starting to comprehend and speak; his motor function did not recover, he remains physically handicapped by spasticity and uses a wheelchair.

Patient 9 (Ash Al Sh.)

This girl was first seen 7 years ago when she was 6 years old. Two months before referral she had a febrile disease

with headache, generalized seizures and coma. She developed generalized rigidity and reflex opisthotonus. At the referring hospital she was investigated extensively for encephalitis and meningitis, and with detailed blood chemistry tests which failed to reveal aetiology. She woke up from the coma after 1 week and remained aphasic, severely rigid with opisthotonus. She developed dysautonomia with periodically spiking high temperatures, flushes, profuse sweating and tremors. The parents were first cousins and had three normal children. At the time of our first encounter she showed severe rigidity of the upper and lower extremities, with brisk deep tendon reflexes and was unable to walk or talk. Blood and CSF chemistry and neurophysiological tests were normal (see details in the Results section). She was initially placed on L-dopa and carbidopa (100 and 25 mg/day, respectively) with no improvement in her clinical symptoms. The brain MRI indicated high signal intensity in the central part of the heads of the caudate and putamen bilaterally, with some volume loss in the lentiform nuclei (images not shown). Six months after the onset of her disease she was placed on biotin (5 mg/kg/day) with marked improvement within days. Further follow-up was uneventful, with some stuttering and wide-based gait present 2 years later. At that time, we discontinued biotin on a trial basis. Within 1 month, she developed confusion and her school performance dropped. She developed rigidity, and ankle clonus bilaterally, and Babinski's sign with increased deep tendon reflexes in the lower extremities, so biotin was started again. At that time, her psychometric evaluation indicated an IQ of 74. Over the next 5 years she improved with normal neurological examination, no evidence of deficits. Her repeated mental age testing revealed an IQ of 85, at 11 years of age. She is attending a normal school but is 1 year behind, with below-average performance. The father reports that if she misses biotin for a while, she develops mild mental confusion and rigidity of the lower limbs.

Patient 10 (N. Al J.)

This girl was first seen at the age of 7 years, 4 years ago. At the age of 6 years she started to vomit with no apparent cause and developed grand mal seizures. She had to receive ventilatory support for 3 months, and once the encephalopathy subsided she had lost all her milestones, was bedridden and quadriplegic. She remained confused with lapses in memory. She was referred when she developed a second episode of seizures. The parents are first cousins and have two normal children. At the time of initial examination the patient had severe rigidity of lower limbs with mild rigidity in upper extremities. Deep tendon reflexes were normal. There was chorea of the mouth and of the tongue, with spontaneous choreiform movements in the proximal limbs, particularly when agitated. She had truncal titubation and facial motor dyspraxia. She had strabismus. Fundoscopic examination was normal. Blood and CSF chemistry, and bacteriological, viral and neurophysiological studies were normal (see details in the Results section). The brain MRI showed necrosis in the putamen and in the central part of the caudate heads bilaterally (images not shown). Her psychometric assessment indicated an IQ of 54. She was placed on biotin (5 mg/kg/day). Within days, she started to behave normally, talk, walk and regain her memory. She has been followed up for the past 2 years and has never experienced another acute episode. Her present IQ is 69 and she attends a school for the handicapped.

Results

Neurological symptoms

Table 1 summarizes the presenting neurological signs and symptoms of the disease, and those at later stages.

Stage I

The disease starts with confusion and a subacute encephalopathic picture of undefined origin. Vomiting was present in four of the 10 cases; a vague history of preceding febrile illness could be obtained in Patients 4 and 9. However, no clear factor that provoked the disease could be identified.

Stage II

Acute encephalopathy with sudden loss of developmental milestones, inability to swallow, loss of speech or slurred speech, loss of motor function with quadriparesis or quadriplegia developing, and seizures.

Stage III

If the disease is not treated it results in a chronic or slowly progressive encephalopathy with an akinetic mute state, permanent loss of speech and comprehension with eventual death.

When biotin is discontinued, Stage I of the disease reappears, e.g. with confusion and decline in school performance, as best exemplified by the history provided by fathers of Patients 6 and 9. In Patient 1, prolonged discontinuation of biotin caused permanent neurological damage.

At the time of initial examination the most prominent symptoms were dystonia, cogwheel rigidity and, at times, opisthotonus. Other parkinsonian signs, such as drooling and action tremor, were seen rarely; bradykinesia and mask-like face were not observed. Four patients had either supranuclear facial nerve paralysis or external ophthalmoplegia. Pyramidal tract signs, such as quadriparesis or quadriplegia with increased deep tendon reflexes, bilateral ankle clonus and Babinski sign, were almost invariably present (Table 1). Ataxia or gait disturbance and truncal titubations were observed in two patients. The muscle-stretch reflexes were diminished during an acute attack in Patient 4, at which time CSF, blood lactate and peripheral nerve conduction velocities

Table 1 *Presenting neurological signs in acute crisis of biotin-responsive basal ganglia disease*

Neurological sign	Patient									
	1	2	3	4	5	6	7	8	9	10
Stage I disease										
A prodrome of confusion	++	–	+	+	–	+	–	+	–	+
Lethargy progressing to coma	+	–	+	+	+	–	–	–	+	+
Vomiting	–	–	+	–	+	–	–	–	+	+
Stage II disease										
Seizures	+	–	–	+	+	–	–	–	+	+
Dystonia	++	+	++	+	++	+	++	+	+	+
Chorea	++	–	–	–	–	–	–	–	–	+
Cog-wheel rigidity	++	–	++	+	++	+	+	+	++	++
Opisthotonus	++	–	+	–	–	–	–	–	+	–
Dysarthria	++	–	+	+	+	–	+	+	+	+
Dysphagia/drooling	++	–	+	+	+	–	+	+	+	+
Paralysis of seventh nerve	+	–	–	+	–	–	+	–	–	–
Paralysis of gaze	–	–	–	+	–	–	+	–	–	+
Quadriparesis	++	–	–	+	+	–	Hemiplegia	+	++	++
Deep tendon reflexes	4+	Normal	4+	Diminished	4+	Normal	4+	4+	4+	Normal
Babinski/ankle clonus	+	–	+	–	–	–	+	+	+	–
Action tremor	++	–	–	+	–	–	–	–	–	+
Ataxia, truncal titubations	–	–	–	+	–	–	–	–	–	+
Dysautonomia	–	–	–	–	–	–	–	–	+	–
Hypertension	–	–	–	–	+	–	–	–	–	–

Severity is indicated by: –, absent; + to 4+, increasing severity.

were normal. Patient 9 showed distinct signs of central dysautonomia during the acute crisis.

Neuroradiological presentation

The brain MRIs of Patients 1–8 show a uniform appearance (Fig. 1). The brain MRI showed hypo-intensity of the striatum in T_1-weighted images and hyper-intensity of the same regions on T_2-weighted images. These changes consist of bilateral necrosis in the central part of the caudate heads and part or all of the putamen. During the acute crisis, both of these structures showed severe oedema (Patient 1). White matter involvement at the grey–white matter junction was also observed in Patient 1, during the acute crisis. Her brain CT showed hypodensity in the putamen bilaterally and asymmetrically (images not shown).

Body fluid investigations

A large number of laboratory investigations were routinely performed, some during the acute stage of the disease, others, while the patient was stable. These studies included blood count, blood and CSF chemistry, lipid profile and uric acid, lactate, ammonia and pyruvate measurements. Other determinations were: amino acids and carnitine profile by tandem mass spectrometry (Rashed *et al*., 1995), copper, ceruloplasmin and biotinidase (Hayakawa *et al*., 1997), also phytanic acid, very long chain fatty acids, toxicology screen for inorganic and organic compounds, antiphospholipid antibodies, protein carbon and sulphur, light and electron microscopy of leucocyte granulation, blood culture for bacteria, and fungi and viral studies. Urine studies included organic acids (Rashed *et al*., 1994), mucopolysaccharides and sulphur amino acids. CSF studies included chemistry, lactic acid, cell count, protein, oligoclonal bands, PCR on DNA for herpes simplex, routine viral, acid fast bacilli and other bacterial cultures, and where mentioned, other viral studies. In Patients 1, 4, 7 and 8 tandem mass spectrometry and organic acid studies for CSF were normal. The fibroblast cultures were tested for various carboxylase activities (Burri *et al*., 1981). The holocarboxylase synthetase was estimated indirectly by measuring propionyl coenzyme A (CoA) and pyruvate carboxylase activity, after fibroblasts were grown in biotin-deficient versus biotin-supplemented medium (Saunders *et al*., 1979) (Table 2); no significant loss of enzyme activity was observed between the two experimental conditions. Biotin-deficient medium was prepared by the addition of excess avidin (Green, 1963). Lysosomal enzymes in fibroblasts were measured as described previously (Ozand *et al*., 1990). These studies revealed no pathology. All patients had the following neurophysiological studies: EEG, visual, brainstem and somatosensory evoked potentials, peripheral nerve conduction studies, electromyogram and electroretinogram. Unless mentioned otherwise they were within normal limits.

The brain MRI and brain [^{18}F]deoxyglucose-PET was available for all patients. Only findings in brain MRI have been described in detail.

Clinical course

The results in Table 3 show disease occurrence in at least three different ethnic groups. Seventy per cent of the parents

Table 2 *Carboxylase activity in fibroblasts and biotinidase in serum*

Patient	Propionyl CoA carboxylase CO_2 fixed (pmol/mg/min)	Pyruvate carboxylase CO_2 fixed (pmol/mg/min)	Biotinidase (nmol/ml/min)
1	461	583	4.4
2	500	595	4.6
3	604	585	5.3
4	738	600	7.2
5	832	675	5.6
6	1088	585	5.9
7	934	1210	5.4
8	1197	1328	7.1
9	1060	942	4.9
10	672	584	6.2
Normal children			
Mean ± SD	1148 ± 368	1284 ± 467	6.23 ± 1.12
Range	406–1882	573–2217	4.38–8.40

The values obtained in normal children are given for carboxylases ($n = 16$) and for biotinidase ($n = 43$). The results are for fibroblasts grown in biotin-supplemented medium. The values were ~10% lower when biotin-depleted medium was used (results not shown)

Table 3 *Summary of clinical findings in patients*

Patient	Sex	Ethnic origin	Parent's consanguinity	Presenting age (years)	Follow-up (years)	Current status	Deaths of siblings (n)†	Affected‡ children/ total children (n_1/n_2)	Family history of other diseases§
1*	F	Saudi	First cousins	5	10	Crippled; IQ 75; quadriparetic	4	6/10	Not remarkable
2*	F	Saudi	First cousins	3	5	Normal	4	6/10	Not remarkable
3*	F	Saudi	Distant relatives	7	8	Normal	1	3/3	Not remarkable
4*	M	Saudi	Distant relatives	9	8	Normal	1	3/3	Not remarkable
5	F	Saudi	Second cousins	5	6	Normal	5 (first wife) 1 (second wife)	6/10 (first wife) 1/10 (second wife)	One dysmorphic infant
6	M	Yemen	First cousins	1	7	Normal	None	1/2	Brother has Tourette's syndrome; cousin has same disease as patient
7	M	Saudi	First cousins	6	3	IQ 85; normal otherwise	None	1/5	Four siblings died of Sandhoff's disease; two maternal cousins with mental retardation
8	M	Syria	First cousins	14	3	IQ 60; paraparetic	1	2/6	Not remarkable
9	F	Saudi	First cousins	6	7	IQ 85; normal otherwise	None	1/3	Not remarkable
10	F	Yemen	First cousins	7	4	IQ 69; normal otherwise	None	1/3	Not remarkable

*Patients 1 and 2 are siblings, as are patients 3 and 4. †Number of deaths probably due to the same disease. ‡Includes number of deaths presumed due to the same disease. §No history or clinical evidence of a basal ganglia disease in parents or family.

were first cousins. The disease usually begins during preschool age. Although the clinical neurological symptoms and signs disappear, or arrest, upon biotin administration, depending upon when treatment is started in relation to the onset of symptoms, the brain MRI remains unchanged (Fig. 1). In the initial patients, L-dopa, thiamine, carnitine and riboflavin were given without any clear benefit. Once biotin was found to control the disease, other supplements were discontinued and patients were maintained on biotin alone. Patient 2, shown together with her crippled sister Patient 1 in Fig. 2, indicates a normal girl of 8 years, while the degree of basal ganglia degeneration seen on her brain MRI remains impressive (Fig. 1B).

The patients were followed-up for 3–10 years. The disease remains asymptomatic in seven out of the 10 patients at the time of this report. However, the histories of previous deaths in the family suggest that it can be lethal (Table 3). Three crippled patients also support the significant morbidity that

can be caused by this entity. Patient 1 was a nearly normal child before she had a catastrophic event with oculogyric crisis upon discontinuation of biotin, after which episode she never totally fully recovered. Patient 8 remained undiagnosed for nearly 10 months. Review of hospital records of his dead brother also indicated a very similar and undiagnosed disease. Patients 9 and 10 had severe disease that remained without treatment for ~6 months and 1 year, respectively. Patient 9 recovered nearly fully, but Patient 10 is in a school for the handicapped. The low IQ of Patient 7 may be explained by the presence of static encephalopathy in the family; his two maternal cousins have mental retardation of unknown cause.

Discussion

Biotin and CNS function

Biotin is a cofactor for various carboxylases that include propionyl CoA, acetyl CoA, 3-methylcrotonyl CoA and pyruvate carboxylase (Moss and Lane, 1971). Apoenzymes of these carboxylases are converted into holoenzymes by a specific enzyme, holocarboxylase synthetase. Deficiency state of individual carboxylases are well known, and that of holocarboxylase synthetase causes loss of activity of all carboxylases, and is known as multiple carboxylase deficiency (Wolf and Feldman, 1982). Endogenous recycling through biotinidase, the deficiency of which also leads to multiple carboxylase deficiency (Wolf *et al*., 1985), preserves most of the biotin in the body. The deficiency of holocarboxylase synthetase may be biotin-resistant (Wolf and Feldman, 1982), or biotin-responsive (Sweetman *et al*., 1977). Biotinidase activity in human brain and CSF fluid is low, and brain is therefore unable to recycle biotin (Suchy *et al*., 1985). The CNS depends on biotin transferred across the blood brain barrier. In experimental animals, the presence of such a saturable transport system with a K_m (Michaelis–Menten constant) of 100 M has been demonstrated (Spector and Mock, 1987). Approximately 50% of the patients with biotinidase deficiency manifest with myoclonic seizures and hypotonia, which may manifest as early as the first week of life (Wolf, 1995). This suggests that in the absence of a continuous supply of endogenous biotin, the brain is unable to maintain its store of biotin. It has been shown that in biotinidase deficiency, the brain may accumulate lactate (Diamantopoulos *et al*., 1986). However, the biochemical cause of the encephalopathy caused by biotin deprivation, such as the permanent loss of hearing, is not clear.

Neurological picture

Stage I of the disease is associated with subacute encephalopathy, progressing into acute encephalopathy with extrapyramidal and pyramidal signs at Stage II. The cranial nerve involvement and facial palsy might be due to the involvement of all basal ganglia, nigral pathways and upper motor neurons. Dystonia and cogwheel rigidity were uniformly present (Table 1). In untreated patients the disease progresses to death (via Stage III).

Dystonia is the most common extrapyramidal tract disorder in childhood; it may occur as idiopathic, symptomatic with unspecified aetiologies, or as a part of a particular CNS disorder (Segawa, 1993).

The most common syndromes with defined aetiologies include Wilson's disease (Starosta-Rubinstein *et al*., 1987), Hallervorden–Spatz disease (Savoiardo *et al*., 1993) and juvenile Huntington's disease (Savoiardo *et al*., 1991). Among the dystonias of unknown aetiology are L-dopa-responsive dystonia (Nygaard *et al*., 1991), idiopathic torsion dystonia of childhood (Marsden and Harrison, 1974), childhood onset parkinsonism (Narabayashi *et al*., 1986) and benign acute neurological dysfunction associated with destructive lesions of the basal ganglia (Roig *et al*., 1990). The present report adds a new entity to this list.

This biotin-responsive basal ganglia disease is different in many respects from the aforementioned diseases (Table 4). It is familial, and possibly inherited as an autosomal recessive disorder. It is similar in many regards to the disease seen in the patients described by Goutieres and Aicardi, 1982; Kellermann *et al*., 1982; Yasukohchi *et al*., 1986; and Gauthier and Geoffroy, 1991. Its course is benign, as long as biotin is provided. However, in contrast to the lesions seen in these latter patients, the basal ganglia lesions in CNS do not disappear spontaneously or upon biotin therapy. The precipitating event is not necessarily infectious and it can present spontaneously.

The biotin-responsive disease is different from the rare juvenile Huntington's disease, in that the globus pallidus and cerebellum are not affected (Roig *et al*., 1993). In juvenile Huntington's disease, the entire caudate and putamen are destroyed, while only selective regions of striatum are involved in the biotin-responsive disease.

The disease is significantly different from L-dopa-responsive dystonia (Table 4) (Nygaard *et al*., 1991). It has an acute presentation with severe extrapyramidal tract signs that include choreoathetosis, not seen in L-dopa-responsive disease. In contrast to L-dopa-responsive dystonia, the symptoms of the disease do not show diurnal fluctuation. In three patients (1, 3 and 9) the use of L-dopa during the acute attack failed to improve the clinical symptoms. The symptoms of L-dopa-responsive dystonia appear within 0.5–5 days after therapy is discontinued, while in biotin-responsive basal ganglia disease it usually takes 1 month for symptoms to reappear when biotin is discontinued.

A comparison of the present patients with idiopathic torsion dystonia of childhood also indicates significant differences. While biotin-responsive disease shows tremor, rigidity and hyperreflexia during crisis, these signs are usually absent in the latter (Table 4) (Marsden and Harrison, 1974).

The disease differs from childhood-onset parkinsonism, since it occurs acutely with severe rigidity at rest and may be associated with choreoathetosis (Table 4) (Narabayashi *et al*., 1986). Some cases of L-dopa-unresponsive dystonia

Table 4 *Comparative clinical, neurological and neuroradiological findings in extrapyramidal tract diseases of childhood*

Symptoms	Biotin-responsive disease	Dopa-responsive disease	Idiopathic dystonia of childhood	Childhood parkinsonism	Post-infectious, benign, acute basal ganglia destruction
Initial sign	Present: confusion, sub-acute encephalopathy	None	None	None or febrile disease	An infectious process
Presenting sign	Extrapyramidal and pyramidal tract disease, dementia	Pyramidal tract signs at times	Extrapyramidal tract signs	Extrapyramidal tract disease	Extrapyramidal tract disease
Dystonia	Present Present	Present	Present	Present	
Chorea	Present, often involving the face	Severe	Absent	Absent	Absent
Rigidity	Cog-wheel rigidity always present	Present at rest and when active	Absent	Present at rest and when active	Present
Hyperreflexia	Present at times with Babinski's sign and ankle clonus	Present, paralleling the degree of rigidity	Absent	Sometimes present, paralleling the degree of rigidity	Present
Coma	Always accompanies the acute crisis	Absent	Absent	Absent	Present
Seizures	Usually present	Absent	Absent	Absent	Absent
Dysarthria	Present during initial or acute presentation	Absent	Absent	Absent	Common
Tremors	At times present	Rare	Absent	Early sign	Not reported
Fluctuating symptoms	No	Diurnal variation	No	No	No
Therapeutic response	Biotin	Dopa	Mild response to dopa	Mild response to dopa	Not studied
Neuroradio-logical changes	Present in early disease, remains unchanged	Not described	Not described	Not described	At times disappear within 1 month

with parkinsonism might be clinical variants of juvenile parkinsonism (Hanakawa *et al*., 1996). In these later instances, brain [^{18}F]glucose-PET shows decreased regional glucose uptake bilaterally only in the putamen, and not in the caudate nuclei.

Other extrapyramidal tract diseases with mitochondrial involvement or Leigh's subacute encephalomyelopathy (Pavlakis *et al*., 1984; Nigro *et al*., 1990) usually show either peripheral or CSF lactic acidosis, optic atrophy and other signs of a mitochondriopathy, such as delayed peripheral nerve conduction time. None of these are associated with the biotin-responsive disease.

Neuroradiological appearance

The brain MRI (Fig. 1) always shows bilateral lesions in the centre of caudate heads and complete or partial involvement of the putamen. The globus pallidus is never involved. Some discrete changes were observed in the thalami, and when the disease is advanced, there is patchy white matter disease (Fig. 1A) (Table 4). It is interesting to note that brain MRI changes of a similar severity were observed in a minimally symptomatic sibling (Patient 2, Fig. 1B). Brain MRI findings resembling those shown in Fig. 1 were, at times, seen in other children who did not respond to L-dopa or biotin. However, the distribution of lesions within the caudate head and putamen in these instances was significantly different.

While the patients remained on biotin, the brain MRI remained unchanged, still showing evidence of caudate head and putamen necrosis (Fig. 1). This is in contrast to neuro-radiological studies in patients with acute destructive lesions of the basal ganglia, i.e. the so-called benign form of infantile bilateral striatal necrosis, in which the basal ganglia lesions might return either to normal or atrophy (Roig *et al*., 1990).

Aetiology

A large number of tests designed to reveal storage diseases, infectious process, mitochondrial diseases and toxicological damage, as outlined in body-fluid investigations, failed to reveal aetiology. No evidence has been obtained for a toxic cause, an autoimmune disease, or for a vascular cause. Basal ganglia vascularization in experimental animals is near the average for cortical grey matter. However, developing basal ganglia are highly susceptible to metabolic insults involving energy metabolism or neurotoxins (Pranzatelli *et al*., 1994; Pranzatelli, 1996).

The only consistently abnormal findings were in brain MRI studies which indicated a selective destruction of the centre of caudate heads and parts of the putamen bilaterally. Although the disease described is biotin responsive, neither biotinidase in serum nor diverse carboxylases in fibroblasts were abnormal. The brain MRI findings were also different from those seen in biotinidase or multiple carboxylase deficiencies. In biotinidase deficiency, the neuroradiological changes indicate diffuse low attenuation of the white matter

followed by progressive marked cerebral atrophy (Bousounis *et al*., 1993). In pyruvate carboxylase deficiency, there are diffuse white matter changes involving brainstem and subcortical white matter (Higgins *et al*., 1994; Pineda *et al*., 1995), and neuropathological studies indicate extensive necrosis of grey matter (Gilbert *et al*., 1983). Only in a minority of severe phenotypes of propionic acidaemia is there entire caudate head and lentiform nuclei loss (Brismar and Ozand, 1994). The appearance of the brain MRI in these latter patients is different from those shown in Fig. 1.

The aetiology of the disease is not clear; an aspect of biotin metabolism yet to be established appears to be deranged. The 10 patients in this study came from three different ethnic groups and seven different families. Diverse ethnic and geographic origins of the patients as well as the absence of exposure to toxic substances, the normal results in chemical tests for organic and inorganic toxic compounds and the familial occurrence suggest that the disease is inherited. The parents did not show evidence of basal ganglia disease, and the numbers of affected children, including those who died presumably of the same disease, suggest an autosomal inheritance. No linkage could be ascertained through clinical studies. The family who had other children with Sandhoff's disease is from a Saudi tribe, among whom the disease is prevalent (Ozand *et al*., 1990). The brother of Patient 6, who developed Tourette's syndrome, had a normal brain MRI; linkage of the two entities cannot be claimed. Recent studies suggest that susceptibility to Tourette's syndrome is complex and is conveyed by a major locus in combination with a multifactorial background (Walkup *et al*., 1996). A prolonged period of follow-up (Table 3), a reasonably uniform neurological presentation (Table 1), control of the disease with biotin and relapses when it is not given, and the uniform appearance of the brain MRI (Fig. 1), all suggest that biotin-responsive basal ganglia degeneration is a distinct novel disease.

Despite the extensive damage observed on the brain MRI, a patient with biotin-responsive encephalopathy remains asymptomatic under treatment. This observation suggests that enough tissue may be preserved in the target areas of the disease, to permit neurological function. Normal carboxylases and biotinidase values suggest the disease might be caused by a defect in the biotin transporter system across cerebral capillaries at the blood–brain barrier. The high doses of biotin used for treatment might have assured some biotin transport into brain by non-specific diffusion (Spector and Mock, 1987).

It is important to check for the presence of this disease in children with acute onset extrapyramidal symptoms as it can be managed without further neurological deterioration.

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