The Clinical Phenotype of Succinic Semialdehyde Dehydrogenase Deficiency (4-Hydroxybutyric Aciduria): Case Reports of 23 New Patients

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ABSTRACT. Objectives. To further define the clinical spectrum of the disease for pediatric and metabolic specialists, and to suggest that the general pediatrician and pediatric neurologist consider succinic semialdehyde dehydrogenase (SSADH) deficiency in the differential diagnosis of patients with (idiopathic) mental retardation and emphasize the need for accurate, quantitative organic acid analysis in such patients.

Patients. The clinical features of 23 patients (20 families) with SSADH deficiency (4-hydroxybutyric aciduria) are presented. The age at diagnosis ranged from 3 months to 25 years in the 11 male and 12 female patients; consanguinity was noted in 39% of families.

Outcome Measurements. The following abnormalities were observed (frequency in 23 patients): motor delay, including fine-motor skills, 78%; language delay, 78%; hypotonia, 74%; mental delay, 74%; seizures, 48%; decreased or absent reflexes, 39%; ataxia, 30%; behavioral problems, 30%; hyperkinesis, 30%; neonatal problems, 26%; and electroencephalographic abnormalities, 26%. Associated findings included psychoses, cranial magnetic resonance or computed tomographic abnormalities, and ocular problems in 22% or less of patients. Therapy with vigabatrin proved beneficial to varying degrees in 35% of the patients. Normal early development was noted in 30% of patients.

Conclusions. Our data imply that two groups of patients with SSADH deficiency exist, differentiated by the course of early development. Our recommendation would be that accurate, quantitative organic acid analysis in an appropriate specialist laboratory be requested for any patients presenting with two or more features of mental, motor, or language delay and hypotonia of unknown cause. Such analyses are the only definitive way to diagnose SSADH deficiency; the diagnosis can be confirmed by determination of enzyme activity in white cells from whole blood. We think that increased use of organic acid determination will lead to increased diagnosis of SSADH deficiency and a more accurate representation of disease frequency. As additional patients are identified, we should have a better understanding of both the metabolic and clinical profiles of SSADH deficiency.

Patients 1997;99:567-574; mental retardation, succinic semialdehyde dehydrogenase deficiency, 4-hydroxybutyric aciduria, hypotonia, ataxia.

ABBREVIATIONS. SSADH, succinic semialdehyde dehydrogenase; GABA, y-aminobutyric acid; MRI, magnetic resonance imaging; EEG, electroencephalogram; CT, computed tomography; EMG, electromyography.

Succinic semialdehyde dehydrogenase (SSADH, EC 1.2.1.24) deficiency (4-hydroxybutyric aciduria, McKusick 271980) is a rare inherited defect in the degradative pathway of the inhibitory neurotransmitter y-aminobutyric acid (GABA).1 Approximately 40 patients have been reported, with a wide variability in clinical phenotype.2 This disorder is unusual because it is a defect of neurotransmitter metabolism.
TABLE. Clinical Findings in 23 Patients With Succinic Semialdehyde Dehydrogenase Deficiency

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at Diagnosis</th>
<th>Ethnicity</th>
<th>Consanguinity</th>
<th>Neontal Problems</th>
<th>Normal Early Development</th>
<th>Mental Delay</th>
<th>Motor Delay</th>
<th>Language Delay</th>
<th>Ataxia</th>
<th>Hypotonia</th>
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<td>A.E.-M.</td>
<td>M</td>
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<td>Palestinian-Lebanese</td>
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<td>-</td>
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<td>+‡‡</td>
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<td>+‡</td>
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<td>B.E.</td>
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<td>Syrian</td>
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<td>-</td>
<td>+§§</td>
<td>+‡‡</td>
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<td>-</td>
<td>-‡‡</td>
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<td>+‡‡</td>
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<td>-‡‡</td>
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<tr>
<td>E.G.</td>
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<td>8 y</td>
<td>Dutch</td>
<td>+</td>
<td>-</td>
<td>-§‡</td>
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<td>-</td>
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</tr>
<tr>
<td>I.C.</td>
<td>M</td>
<td>2 y</td>
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<td>-</td>
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<td>+‡‡</td>
<td>+‡‡</td>
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<td>6 y</td>
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<td>-‡‡</td>
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<tr>
<td>J.I.Y.</td>
<td>F</td>
<td>8 y</td>
<td>Korean</td>
<td>-</td>
<td>+§</td>
<td>+‡‡</td>
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<tr>
<td>K.S.</td>
<td>F</td>
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<td>-‡‡</td>
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<td>M.H.‡</td>
<td>M</td>
<td>3 mo</td>
<td>Saudi</td>
<td>-</td>
<td>+‡</td>
<td>+‡‡</td>
<td>-</td>
<td>-‡‡</td>
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<td>+‡‡</td>
<td>+‡‡</td>
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<tr>
<td>M.S.</td>
<td>F</td>
<td>3½ y</td>
<td>Pakistani</td>
<td>+</td>
<td>+‡</td>
<td>+‡‡</td>
<td>-</td>
<td>-‡‡</td>
<td>-‡‡</td>
<td>+‡‡</td>
<td>-‡‡</td>
</tr>
<tr>
<td>M.W.</td>
<td>M</td>
<td>4½ y</td>
<td>American-European</td>
<td>-</td>
<td>-‡‡</td>
<td>+‡‡</td>
<td>+‡‡</td>
<td>+‡‡</td>
<td>+‡‡</td>
<td>+‡‡</td>
<td>+‡‡</td>
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<tr>
<td>N.O.</td>
<td>M</td>
<td>12 y</td>
<td>Bulgarian</td>
<td>-‡‡</td>
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<td>+‡‡</td>
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<td>-‡‡</td>
<td>-</td>
<td>-‡‡</td>
</tr>
<tr>
<td>P.F.</td>
<td>F</td>
<td>4 y</td>
<td>Inuit (Greenland)</td>
<td>-</td>
<td>+‡‡</td>
<td>+‡‡</td>
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<td>+‡‡</td>
<td>+‡‡</td>
<td>+‡‡</td>
<td>+‡‡</td>
</tr>
<tr>
<td>P.L.</td>
<td>M</td>
<td>4 mo</td>
<td>American-European</td>
<td>+‡‡</td>
<td>+‡‡</td>
<td>+‡‡</td>
<td>+‡‡</td>
<td>+‡‡</td>
<td>+‡‡</td>
<td>+‡‡</td>
<td>+‡‡</td>
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<tr>
<td>P.S.H.†</td>
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<td>+‡‡</td>
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<td>+‡‡</td>
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<td>Indian</td>
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</tr>
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<td>P.V.‡</td>
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<td>+‡‡</td>
<td>+‡‡</td>
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<td>+‡‡</td>
<td>+‡‡</td>
<td>+‡‡</td>
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<tr>
<td>T.A.</td>
<td>M</td>
<td>6½ y</td>
<td>Lebanese</td>
<td>+</td>
<td>+‡‡</td>
<td>+‡‡</td>
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<td>+‡‡</td>
<td>+‡‡</td>
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<td>Y.A.</td>
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<td>2 y</td>
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<td>+</td>
<td>+‡‡</td>
<td>+‡‡</td>
<td>+‡‡</td>
<td>+‡‡</td>
<td>+‡‡</td>
<td>+‡‡</td>
<td>+‡‡</td>
</tr>
</tbody>
</table>

* MRI indicates magnetic resonance imaging; and CT, computed tomography.
† First cousins.
‡ Presenting signs.
§ See "Case Reports."
|| Siblings.
¶ Siblings.

as well as one in which the accumulated diagnostic metabolite, 4-hydroxybutyric acid, also has unique neuropharmacologic properties (Table). Most patients show some degree of retardation in psychomotor and language development, often associated with hypotonia and/or ataxia. The difficulty lies in detection, because the disorder presents with such nonspecific neurologic features that most neurologic or metabolic specialists are unlikely to request organic acid quantification. Without such analyses, these patients remain undiagnosed. Some of the patients we studied were initially examined for cerebral palsy or fragile X syndrome. Our review of these patients led us to suggest the existence of two distinct groups of SSADH-deficient patients, those with normal early development and others with developmental problems during infancy.

METHODS

Urinary organic acid analysis identified increased excretion of 4-hydroxybutyric acid in all patients (except P.S.H., who died at 13 years of age and whose diagnosis was deduced based on clinical features similar to those of her diagnosed siblings). Other metabolites consistent with the further metabolism of 4-hydroxybutyric acid, including 3-hydroxypropionic acid, 3,4-dihydroxybutyric acid, and glycolic and 4,5-dihydroxyhexanoic acids, were identified in increased amounts in the urine of many patients. Deficiency of SSADH activity was demonstrated in extracts of lymphocytes, lymphoblasts, and/or fibroblasts derived from all patients (except P.S.H.).

CASE REPORTS (See Table)

Unless otherwise stated, all pregnancies and deliveries were normal, and children were nondysmorphic with normal somatic growth and no associated movement disorder other than ataxia. Pertinent abnormalities are given.

A.E.-M.

A.E.-M. was the third child born to consanguineous (first cousins) Palestinian-Lebanese parents and first cousin to M.H. At 4 months of age he presented with generalized hypotonia, which was more pronounced in the upper extremities. Hypertelorism and epicanthal folds were evident. He was almost developmentally and mentally normal by the age of 11 months, having only mild hypotonia and moderate hepatomegaly.

A.F.

A.F. first presented at 25 years of age. He was born to nonconsanguineous Chinese parents. His early cognitive and language development were normal, with first words at 10 months and full sentences by 2 years of age. His motor milestones were delayed; he did not walk until 2 years of age. At 3 to 5 years of age, A.F. was described as lacking coordination, motor control, and social skills. He entered primary school but repeated the first grade. A psychologic evaluation, conducted at 9 years of age in the United States, determined that the patient...
TABLE. Clinical Findings in 23 Patients With Succinic Semialdehyde Dehydrogenase Deficiency

<table>
<thead>
<tr>
<th>Patient</th>
<th>Reflexes</th>
<th>Ocular Problems</th>
<th>Behavioral Problems</th>
<th>Hyperkinesis</th>
<th>Psychosis</th>
<th>Seizures</th>
<th>Electroencephalogram</th>
<th>Neuroimaging*</th>
<th>Carnitine</th>
<th>Treatment with Vigabatrin</th>
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<td>A.E.-M.†</td>
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<td></td>
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<td></td>
<td>Normal</td>
<td>MRI normal</td>
<td>Ineffective</td>
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<tr>
<td>A.F.</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Normal</td>
<td>Normal</td>
<td>MRI normal</td>
<td>Ineffective</td>
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<td>B.E.</td>
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<td>—</td>
<td>—</td>
<td>+§</td>
<td>—</td>
<td>+§</td>
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<td>MRI normal</td>
<td>Ineffective</td>
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<td>+§</td>
<td>—</td>
<td>+§</td>
<td>+§</td>
<td>Normal</td>
<td>Abnormal</td>
<td>CT§</td>
<td>Low</td>
<td>Effective§</td>
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<td>+</td>
<td>+</td>
<td>—</td>
<td>+/§</td>
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<td>J.L.Y. †</td>
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<td>Abnormal</td>
<td>Abnormal CT§ MRI normal</td>
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</table>

had minimal brain dysfunction. He was then placed in a special education program. During adolescence he had grand mal seizures but has remained seizure-free while taking carbamazepine (Tegretol) and primidone (Mysoline).

At 22 years of age, after completion of a special education program in the United States, the patient returned to Hong Kong and began to have symptoms of psychosis and hallucinations, which were successfully treated with haloperidol (Haldol). Genetic evaluation at 25 years of age revealed an uncooperative, psychotic, bilingual man with tall stature, macrocephaly, and a long, triangular face. He had a complex partial seizure disorder. Neurologic examination was nonfocal, cranial magnetic resonance imaging (MRI) showed no abnormalities, and the electroencephalographic background was diffusely slow. Vigabatrin therapy was ineffective.

B.E.

B.E. was born to nonconsanguineous Turkish parents. Her psychomotor development was retarded; she walked at 30 months with an unsteady gait. Developmental tests at 5 years of age placed her at a 15- to 18-month developmental level. Her speech development was poor; her vocabulary consisted of only a few words. Neurologic examination results were normal and did not show ataxia or hypotonia. Alternating strabismus was noted. Vigabatrin therapy, attempted for 2 months without clinical effect, was discontinued.

B.H.

B.H., a Syrian boy born to consanguineous parents (cousins), presented at 19 months of age for evaluation of hypotonia since the age of 2 months. He has three siblings who are well and have no developmental problems. The mother received antibiotics and benzodiazepines for leg pain during the fifth and sixth months of pregnancy. The child had a history of recurrent respiratory distress and had three previous hospital admissions for chest infections, one associated with tonic-clonic movements (which may have been related to an aminophylline overdose). Developmentally, he had no formed words at 19 months. Although he was slow to feed, there were no problems with swallowing or vomiting. He had extreme hypotonia with marked head lag, laxity of ligaments, and absent reflexes.

A muscle biopsy revealed nonspecific type 2 atrophy. MRI showed no abnormalities and a minor increase in signal in the white matter posterolateral to the lateral ventricles.

After starting vigabatrin therapy, the patient made slow but definite improvement. Of note was the immediate cessation of hospital admissions for respiratory infections. The patient's breathing remained normal, he became more responsive and playful, and his head control improved; however, he remained hypotonic and developmentally delayed. At 2½ years of age, he sat on his own and began to crawl, although his speech consisted of monosyllables. At 3 years of age, he crawled on all four limbs but remained hypotonic and areflexic.

C.S.

C.S., an American-European girl, presented for evaluation at 10 months of age. She was born after a pregnancy complicated by hyperemesis gravidarum requiring total parenteral nutrition and preterm labor at 32 weeks' gestation. At 7 months of age, she was admitted to the hospital after an accident in which she sustained
a subgaleal hematoma and a right parietal skull fracture, with resulting subtle left hemiparesis. Early development was normal; she rolled at 6 months and sat alone at 10 months.

She had a generalized seizure at 11 months of age. An electroencephalogram (EEG) was normal; MRI of the brain was reported with diffuse hyperintensity in the deep subcortical white matter, most likely reflecting some type of dysmyelination or demyelinating process.

His examination was significant for subtle signs of left hemiparesis. She had mild developmental delay. She had good movement of all extremities and good muscle tone and coordination.

D.E.

D.E. presented at 7 years of age. This German boy had the developmental age of 2½ to 3 years with respect to perception, fine-motor activity, social behavior, and language comprehension. His expressive language abilities were even more developmentally retarded. Hyperactivity limited his concentration span to less than 2 minutes. He may have had a few very short astatic seizures. The EEG showed an abnormal background rhythm with multifocal sharp and slow-wave foci over both hemispheres, which were more pronounced in the frontal and occipital regions. Neuroimaging, including computed tomography (CT) showed that the left ventricle was slightly enlarged; no other brain anomalies were detectable, and the cerebrospinal fluid was normal. The patient’s plasma showed a deficiency of carnitine with a total carnitine level of 4.9 μmol/L.

The patient had slight hypertrophy of the left cardiac ventricle. Vigabatrin treatment was given with increasing doses of up to 1250 mg/d (100 mg/kg per day). The medication was well tolerated and led within 1 month to a reduction of hyperactivity and an improvement in concentration and cooperation.

E.G.

E.G., an 8-year-old Dutch girl, presented with mental retardation and epilepsy. Her parents were consanguineous (first cousins). She walked at 15 months, but speech development was much delayed. The first grand mal seizure occurred when she was 6 years old. She was admitted to a school for severely retarded children.

Medical examination at 8 years of age showed mild, generalized hypotonia with a flexed gait and poor associated arm movements. No pathologic reflexes could be elicited. Ophthalmologic and hearing examinations did not reveal any abnormalities. She could follow only simple instructions and had poor verbal abilities.

The EEG and MRI did not reveal any abnormalities. Laboratory analysis showed normal cerebrospinal fluid and normal chromosomes. The patient was treated with vigabatrin at a dose of 500 mg/d. After 20 months, a follow-up examination showed that her condition improved, and she no longer had seizures.

I.C.

I.C., an American boy born to nonconsanguineous parents of European heritage, was hospitalized at 2 months of age for evaluation of a 1-month history of chronic bloody diarrhea with mucus, which subsequently resolved. He underwent surgery for bilateral strabismus at 18 months. Developmentally, he completed all gross-motor, fine-motor, and language milestones up to 1 year of age.

Before he started walking independently (11 to 12 months of age) he had an apparent lack of balance, with frequent falling and bumping into objects. At 23 months he sustained a head injury in a fall; 3 weeks later he was evaluated for ataxia. Developmentally, the patient had a 30-word vocabulary but did not combine words. He was able to climb stairs, used a cup and spoon, assisted with dressing, and scribbled with a pencil on paper. He exhibited appropriate social interaction with the ability to follow multiple-step commands.

At examination he had a vascular telangiectasia of bulbar conjunctiva with no cutaneous telangiectasia and no other neurocutaneous stigmata. Neurologic examination revealed optokinetic nystagmus present in both horizontal directions and ratchet tracking of objects with both eyes. The patient had normal strength in all extremities with normal muscle bulk and normal to slightly diminished muscle tone throughout his body. His stance was slightly broad based for his age, with a tendency to walk on his toes; his gait was clearly ataxic without a directional component. He fell frequently when attempting to walk, run, or stoop to recover objects. The patient also had symmetric appendicular ataxia with associated dysmetria. No tremor was present, and deep-tendon reflexes were normal.

MRI (the brain showed no abnormalities. Physical therapy evaluation placed him at an 18- to 22-month motor development level. There was spontaneous improvement of his truncal and gait ataxia; he did not fall when he walked, ran, or stooped to recover objects. At 32 months, his motor skills were progressing, his memory was good, and he was speaking in short sentences.

Family history was significant for a maternal sister with hydrocephalus and developmental delay who died at 33 years of age. In addition, a paternal cousin reportedly had developmental delay of uncertain cause.

The patient started receiving vigabatrin at 50 mg/kg per day. While receiving vigabatrin therapy, the patient’s ataxia improved, along with other aspects of his development, which were documented by neuropsychologic studies before and after treatment. The patient has had no adverse affects from vigabatrin therapy.

I.O.

I.O. presented at 11 months of age for evaluation. She was born to consanguineous parents of Turkish descent and has two older, healthy siblings.

At 5 months, the infant had febrile pneumonia accompanied by seizures. Her EEG and cranial sonogram were normal, and her recovery was uncomplicated. At 8 months of age, she had noticeable motor development retardation, muscular hypotonia, and a low activity level. In addition, physical examination revealed hypotonia. MRI of the brain was consistent with that of a 6-month-old with a slightly widened subarachnoidal space. After diagnosis, vigabatrin therapy was started with a 250-mg dose three times a day.

Two months after the initiation of vigabatrin therapy, the child showed increased agility and stood briefly with help. The hypotonia was reduced to normal. After 1 year of treatment with vigabatrin and physical therapy, she had muscular hypotonia with delayed motor and language development. An increase in the vigabatrin dose temporarily caused agitation and screaming. The child also received a carnitine supplement because of her chronically low carnitine level.

J.E.Y.

J.E.Y. (the Korean female sibling of J.I.Y.) presented at 6 years of age. She was born 2 to 3 months premature and had a birth weight of approximately 2 lb. The mother reported exposure to dry cleaning chemicals during the pregnancy with no other obvious teratogenic exposures. The infant was in neonatal intensive care for 2 months for feeding and growth, during which time there were no significant problems associated with prematurity. Early developmental milestones seemed normal; however, her speech was delayed with her first words at 2 years of age.

At 6 years of age, the patient had a 20-word vocabulary and attended a school for behavioral problems. The patient did not have self-injurious behavior to the same degree as her sister (J.I.Y.), but she had done a lot of picking at her skin. The patient also had some initial hypotonia, although it was minimal.

J.E.Y.

J.E.Y. (the older Korean female sibling of J.E.Y.) presented at 8 years of age. She reportedly had normal early developmental milestones. She walked at approximately 1 year of age, and had minimal language development at 3 years of age. The child's development was extremely slow, although she had no loss of developmental milestones. She had problems with hyperactivity and self-injurious behavior. Her 30-word vocabulary consisted of a mixture of English and Korean. She has attended primary school the past 3 years.

K.S.

K.S., a Turkish girl, presented at 2 years of age for evaluation of delayed development. She has an older sister who is healthy. Developmentally, she sat at 10 months and walked at 20 months. Clinical examination showed mild muscular hypotonia and hy-
porexenia. After the diagnosis of SSADH deficiency, vigabatrin therapy was started.

At 5 years of age, she had received 75 mg/kg vigabatrin for more than 24 months with no side effects. There was little progress in mental development; her developmental level was approximately that of a 2-year-old. She spoke only a few German words and some short sentences in Turkish. Her physical progress was poor, although she was able to walk and run slowly.

In 1992, her cranial MRI showed no abnormalities. In February 1996, symmetric lesions in the globus pallidus, thalamus, and brain stem were identified. The clinical profile has not changed since the last examination.

M.H.

M.H., a Saudi Arabian boy (first cousin to A.E.-M.), was born to consanguineous parents (first cousins) and has two older, healthy siblings.

At 3 months, the patient had generalized hypotonia. At 4 months, after hospital admission, he was found to have severe hypotonia and areflexia with poor head control and was unable to raise his head when lying in the prone position. The child seemed alert and interested in his surroundings.

Treatment with vigabatrin began at 9 months of age, and the dose was gradually increased to 100 mg/kg. He made progress while receiving this treatment. Although head control remained poor, the patient almost sat by himself at 10 months of age. At 16 months, he walked with support and spoke a few words, and his deep-tendon reflexes were normal.

M.S.

M.S., a 3½-year-old Pakistani girl, presented after a generalized tonic-clonic seizure associated with fever. During the subsequent 24 hours the patient seemed confused and frightened, suggesting encephalopathy. During the next 48 hours, she showed gradual improvement but was then noted to have an unsteady, wide-based gait and a tendency to fall. There were also associated choreiform movements. The patient continued to improve during the ensuing 4 days.

She was born to consanguineous parents (first cousins) whose family history was significant for seizures and mental retardation in both the father's and mother's families. The patient has a healthy, older male sibling.

As an infant, she was a weak and poor feeder. Her development was delayed; she sat unaided at 10 months, rolled at 11 months, and began to speak at 20 months. Previous neurologic evaluation failed to reveal a cause.

Reexamination revealed a marked general intellectual delay. Her gait was immature and wide based with normal tone and reflexes. The patient had a deepened pitch on her left abdo-

men. CT showed generous subarachnoid spaces around the base of the brain, and the fourth ventricle was large. Her EEG was normal.

At examination at 4 years 8 months, the patient still had delay in her psychomotor development. She was able to string two to three words together in both English and her native tongue. Her play was immature, reflective of a child 18 months to 2 years of age. The patient was not toilet trained. She was generally hypo-
tonic with preserved reflexes. She had frequent involuntary move-

ments, predominantly of the upper limbs.

At 7½ years the patient had good situational understanding and was speaking in simple sentences but was still clumsy. Before initiating vigabatrin therapy, the patient had hallucinations, which were primarily visual. These stopped when she began treatment.

With continued treatment, her ataxia also improved.

M.W.

M.W. presented at 4½ years with significant hypotonia, speech delay, motor delay, and moderate mental retardation. His non-

consanguineous parents were of European ancestry. During early infancy, the patient had problems with vomiting associated with feeding. The patient underwent surgical correction of pyloric stenosis at 8 weeks of age. Frequent episodes of otitis media required multiple myringotomy tube placements and chronic antibiotic therapy. He also had frequent episodes of tonsillitis and under-

went a tonsillectomy and adenoidectomy at 4 years of age. At 4½ years, he had significant hypotonia, speech delay, motor delay, and moderate mental retardation.

The patient had generalized hypotonia at 4 months, and his motor development was significantly delayed; he sat at 10 months, pulled to stand at 14 months, and walked at 21 months. At 2½ years the patient was referred to a neurologist, who confirmed marked generalized hypotonia without definitive diagnosis. An EEG, electromyography (EMG), and CT of the head were normal. He had an 18- to 20-word vocabulary but was unable to combine words to form sentences. Developmental testing at 2½ years of age determined the patient's gross-motor skills to be at the 15-month level, fine-motor skills to be at the 12-month level, receptive lan-
guage skills to be at the 10- to 12-month level, expressive language skills to be at the 12- to 14-month level, and overall cognition to be at the 12-month level.

Evaluation at 4½ years revealed that the child was not toilet trained and was just learning to run. He was unable to dress himself and was unable to use utensils to feed himself, although he could finger feed. Speech and language development also were delayed significantly. He had a 100-word vocabulary and could combine them into two- and three-word sentences. Examination was significant for generalized hypotonia and laxity of joints, with overall decreased muscle tone but intact deep-tendon reflexes. A short (proximal) phalanx on the fifth digit of the right hand was also noted.

The patient's plasma showed a deficiency of carnitine, with a total carnitine level of 24 nmol/mL (normal, 35 to 50 nmol/mL), a free carnitine level of 20 nmol/mL (normal, 30 to 45 nmol/mL), and a short-chain acylcarnitine level of 4 nmol/mL (normal, 2 to 6 nmol/mL). After treatment with L-carnitine at 30 mg/kg per day, the patient's muscle tone improved dramatically. His speech and articulation also improved. Results of a subsequent analysis of plasma carnitine levels were within the normal range. Another examination after 2 months of L-carnitine therapy showed essentially normal muscle tone and strength.

N.O.

N.O. was born to nonconsanguineous Bulgarian parents. He began walking at 12 months and began speaking at 2 years of age, although he never exceeded three-word sentences. His motor development was normal, except for problems with small motor function and slight ataxia. He was hyperkinetic and was unable to concentrate for more than 10 minutes. He did not sleep through nights and often ground his teeth during sleep.

At 12 years of age, school entrance testing with nonverbal test material revealed a mental development age of 3½ years. His ability to communicate was severely hampered by his language disabilities, which included stuttering, repetitions, and a minimal vocabulary. Later in his development, he was able to understand both German and Bulgarian. He was hyperactive and had some minor fine-motor deficits, which occasionally were noticeable. The EEG was irregular and slow, and MRI showed only a few non-specific hyperintensive signals in the area of the left globus palli-
dus. High doses of vigabatrin improved the patient's condition but induced electroencephalographic changes and seizures. Lower doses were better tolerated. A report of vigabatrin therapy in this patient is presented elsewhere.

P.F.

P.F. was born in Greenland and is ethnically Inuit. Her psy-

chomotor development generally was retarded; she walked at 2½ years of age. At 4 years of age, she ran, spoke three- to four-word sentences, and understood what was said to her. Her muscle tone was slightly decreased, and she had weak reflexes. Her eye exam-

ination revealed mild strabismus.

P.L.

P.L. was the male child of nonconsanguineous American par-

ents of European heritage. At 4 months of age, lethargy de-

veloped, which was associated with emesis, hypotonia, and a dis-
tended bladder.

At examination, his weight was in the 5th percentile, height was in the 10th percentile, and head circumference was in the 60th percentile. He was thin and pale, with a marked absence of subcutaneous fat. Motor examination revealed marked truncal and appendicular hypotonia; however, no atrophy or fasciculations
were seen. Deep-tendon reflexes could not be elicited. An EEG, MRI, and EMG nerve conduction studies were normal.

After diagnosis, the 4-month-old started receiving vigabatrin at 50 mg/kg per day. seizures decreased during the subsequent months to 100 mg/kg per day. The infant was clinically reevaluated at 13 months of age and found to be thriving. His weight was in the 91st percentile, height was in the 93rd percentile, and head circumference was in the 65th percentile. Neurologically, there was no evidence of hypotonia, and his examination results were nonfocal. Developmentally, he was sitting without support and eating both formula and baby foods. He could reach for and transfer objects, clap his hands, and say a few nonspecific words.

P.S.H. (Note: Diagnosis Deduced After Death Because of Two Affected Siblings)

P.S.H. was the first child born to a nonconsanguineous Indian couple. The mother had a slight build and a somewhat unstable, atatic gait. At 3 months, PSH had poor head control and general muscular hypotonia. At 11 months, the child sat alone but had poor reflexes. The EEGs revealed multifocal discharges. The patient began having absence seizures at 2 years of age. Psychomotor development was severely delayed; the child stood alone at 18 months of age, walked alone at 2½ years of age, and spoke only one or two words by 3 years of age. The parents reported that the child was restless, had difficulty concentrating, and often missed objects when attempting to grab them.

Examination and clinical studies revealed no neurodegenerative or metabolic disorders. Treatment with valproic acid resulted in increased alertness and balance, and seizures became less frequent and finally ceased. The valproic acid treatment was discontinued at 10 years of age after 5 seizure-free years. Approximately 1 year later, generalized epileptic seizures recurred and continued with increasing frequency. The child rapidly lost all psychomotor abilities and died at 13½ years of age.

P.S.

P.S., the younger female sibling of P.S.H., presented at 9½ years for evaluation. During her first few months, she reportedly had delayed motor development, poor head control, and general muscular hypotonia. She sat alone at 12 months, stood at 18 months, and walked at 20 months.

She began having absence seizures at 4½ years of age; phenobarbital briefly reduced the frequency of the seizures. Grand mal seizures started when the patient was 7 years old and were treated with valproic acid.

At examination, the patient was friendly and alert and tried to follow simple directions, but she was restless and unable to concentrate. She spoke only one or two words. The patient’s skeletal age was retarded; her chronological age of 9½ years was compared with her skeletal age of 4½ years. She walked with an atatic gait and uncoordinated gait and could not climb stairs on her own. She had poor fine-motor ability with marked faciodynia, general muscular hypotonia, and hyporeflexia.

The EEG had an abnormal background rhythm and continuous β activity with generalized, irregular spike wave discharges. In addition, multifocal discharges, with separate foci seen over both hemispheres, were enhanced by intense photic stimulation. Diagnosis was made because of sibling P.V.

MRI of her brain revealed no abnormalities at 10½ years of age. Menarche was at 11½ years of age. At 13½ years, her physical development was normal, and her height and weight were in the 25th percentile. There was no further intellectual development, and she was not able to speak, with the exception of a few incomprehensible syllable duplications. She was still unable to follow simple commands, which primarily was because of her severe hyperactivity and limited attention span. She attended a special school for severely retarded children. Her ataxia had not progressed, although she has a wide-based gait. There was no more severe activity with the increased dosage of valproic acid (40 mg/kg per day) beginning September 1994. The EEG had a slightly abnormal background activity but no more discharges and no pathologic reaction to photic stimulation. The initial dosage of vigabatrin was 20 mg/kg per day and was increased during a period of 1½ years to 40 mg/kg per day. During this time, there was no improvement in intellectual ability or behavior. Treatment was discontinued because of disturbing hypersalivation and increasing sleepiness during the day.

T.A.

T.A. was born after a pregnancy complicated by spotting at 5 months and treated with bed rest. The mother also had a 1½-pack-per-day smoking habit. The consanguineous (first cousins) Lebanese parents had two other children, a 16-year-old and a 14-year-old, who were healthy.

As an infant, the patient had trismus and periodic episodes of stiffening, with his head turning to the left and possible back arching. His motor development was delayed; he sat alone at 1½ years, crawled at 2 years, and walked alone at 4 years. He had a slightly unstable, frequent falls. He had a diagnosis of cerebral palsy.

At 1 year of age he was hospitalized for vomiting, fever, and possible dehydration. Neurologic evaluation at 2 years of age attributed his psychomotor retardation to multigenic inheritance because of the parents’ consanguinity. His speech development and comprehension were slow, and his vocabulary was limited to single words. He finger fed and used a cup by 3 years of age, but he did not use a spoon until 5 years of age. He had minimal motor development improvement; although he crawled well and pulled to stand, he could not stand or walk alone. Restlessness and hyperactivity developed, which limited her concentration. She attended a special school for severely retarded children. She has had no grand mal seizures but has had frequent (daily) absence seizures and myoclonic absence seizures.

The seizure frequency could be reduced by treatment with valproic acid and ethosuximide. Vigabatrin treatment has not been attempted.

Y.A.

Y.A. was born to consanguineous Turkish parents. His psychomotor development was delayed; he sat at 12 months, stood at 14 months, and walked alone at 25 months. Speech development also was delayed, with his first words at 3 years. Developmental testing revealed severe retardation.
Neurologic examination revealed convergent strabismus, generalized hypotonia without ataxia, and normal deep-tendon reflexes. CT of the brain and an EMG showed no abnormalities.

He had multiple episodes of clouded consciousness, shouting, and abnormal behavior occurring between the ages of 2 and 3½ years. These episodes generally occurred with fever and were 10 to 15 minutes in duration. His EEG revealed hypofunctional abnormalities, especially posteriorly; however, no epileptic abnormalities were found.

Vigabatrin therapy (50 mg/kg) was initiated at 27 months of age and was increased to 100 mg/kg at 37 months of age. There have been no clear clinical effects of the vigabatrin.

**DISCUSSION**

The presenting problem varied among the patients studied; however, in general, the presenting symptoms were neurologic (Table). The following presenting signs were observed: motor delay, 14 patients; hypotonia, 10 patients; mental delay, 9 patients; language delay, 6 patients; ataxia, 3 patients; seizures, 2 patients; and neonatal problems, 1 patient. All of the patients presented with one (or more) of these symptoms for which the parents sought help. The Table verifies the wide range of phenotypic presentation. Even in sibships, the disease presentation is not completely consistent. For example, J.I.Y. had hyperkinesia, which was not observed in the younger sibling, whereas the younger sibling, J.E.Y., had evidence of hypotonia not seen in her older sibling. In a sibship of three patients, however, the phenotype was very consistent. The lack of a clear-cut presenting phenotype and the significant variability in overall presentation further underscores the variable nature of SSADH deficiency and the relative likelihood that the disorder is frequently undiagnosed or even misdiagnosed.

In our patients, we tabulated the following descents: Turkish, 4; white American, 4; Northern European (German, Dutch, and Bulgarian), 3; Indian, 3; Palestinian (Lebanese), 2; Korean, 2; Syrian 1; Saudi, 1; Inuit (Greenland), 1; Pakistani 1; and Chinese, 1. To date, we know of no patients detected with SSADH deficiency who are in South America or Africa. One of the first patients in whom SSADH deficiency was diagnosed was thought to have originated from Algeria, but it is unclear whether he was French or Algerian by birth. Thus, SSADH deficiency seems to be primarily a disorder of the Eurasian region. Whether a founder effect can be linked to the disease remains to be determined. On the other hand, this may simply reflect more efficient metabolic screening of the pediatric population for inherited disease in the Northern European region. Approximately 40% of the probands in this report are offspring of consanguineous parents, a very high incidence of consanguinity. This may account for a Middle Eastern predominance in the geographic distribution of patients because of cultural habits. On the other hand, it may imply that disease-related alleles are rare in the human population. A high incidence of consanguinity is also consistent with multiple loci, but this will be addressed through molecular genetic studies.

At this time, it is difficult to assess whether "distinct" or "variant" forms of SSADH deficiency disease exist, because the patient population is still too small. The SSADH gene is single copy and has been mapped to chromosome 6p23. However, until we have determined through molecular analysis that the disease maps to this locus in each patient, it remains preferable to refer to variant forms of SSADH deficiency. We do not know whether modifier loci have a role, and it remains possible that heterogeneity may be more than allelic.

One intriguing finding in the tabulation of our patients is the possible distinction of early- and late-onset forms of SSADH deficiency, or at least forms of the disease differentiated by development during infancy. Remarkably, the Table verifies that 7 of 23 patients had normal early development. This is not to say that the ensuing clinical course in these putative "late-onset" patients is mild. Moreover, it is difficult to identify any one factor as the cause of the late-onset disease form. Molecular genetic analyses eventually may provide answers to these questions. Another interesting observation is the fact that therapeutic intervention with the GABA transaminase inhibitor vigabatrin was only clinically beneficial in about one third of patients (Table).

The lack of therapeutic efficacy with vigabatrin is of interest. Therapeutic efficacy may again reflect heterogeneity at the genetic or enzymic level. On the other hand, Howells and colleagues have suggested that vigabatrin has limited use in SSADH deficiency because of differential effects on organ specific GABA transaminases. These investigators postulated that although vigabatrin may inhibit brain GABA transaminase effectively, limited inhibition of peripheral organ GABA transaminases could lead to resupply of 4-hydroxybutyric acid across the blood-brain barrier, thereby decreasing the clinical efficacy of therapeutic intervention in the central nervous system.

Intervention with high-dose vigabatrin actually had deleterious effects in one patient. Accordingly, Matern and colleagues found that titrating the vigabatrin dose to a clinically beneficial level was prudent in their patient with SSADH deficiency. High levels of vigabatrin (75 to 100 mg/kg per day) induced electroencephalographic abnormalities and seizure activity in this patient, whereas lower levels (25 mg/kg per day) were beneficial. For future reference, physicians treating patients with SSADH deficiency may wish to administer vigabatrin in increasing quantities. Interestingly, in the three patients for whom L-carnitine levels were evaluated, the plasma levels were low (Table), and carnitine therapy in M.W. dramatically improved muscle tone. Therefore, L-carnitine intervention should be considered in SSADH deficiency if plasma carnitine levels are low.

This review of 23 new SSADH-deficient patients clearly demonstrates that the clinical phenotype is extremely nonspecific, which suggests that the disorder is significantly underdiagnosed. It is likely that all patients with SSADH deficiency will manifest some degree of psychomotor deficit within their childhood years; however, speech and language delay and hypotonia are not necessary concomitants of the disorder, as previously thought. Although the
findings varied, delayed psychomotor and language development and hypotonia were observed in approximately three fourths of the patients. Notable exceptions were I.C. and A.F. (the latter an adult patient who attended primary school), both of whom had normal development of speech and language. The detection of seizures in half of the patients was surprising, because seizures were not previously thought to be prevalent in SSADH deficiency. On the other hand, the detection of ataxia in only one third of patients was surprising, because ataxia was previously thought to be common in SSADH deficiency. The inability to diagnose SSADH deficiency is exemplified in A.F., in whom the correct diagnosis was not achieved until 25 years of age. Interestingly, this man represents only the second adult patient in whom SSADH deficiency has been diagnosed.9

In addition to a nonspecific clinical presentation, other features of SSADH deficiency may often confound the correct differential diagnosis. Patients with SSADH deficiency do not present with the usual concomitants of an inborn error of metabolism. There is no metabolic acidosis, hyperammonemia, hypoglycemia, growth retardation, or episodic decompensation with vomiting and/or lethargy often seen in other inborn errors of metabolism. In addition, the characteristic metabolite in the disorder, 4-hydroxybutyric acid, can elude accurate quantitation because of its ability to lactonize and volatilize. The essential feature for diagnosis of SSADH deficiency is 4-hydroxybutyric aciduria. However, there has not been 100% concordance between metabolite excretion and enzyme deficiency thus far, although the percentage is very high. We are aware of at least two patients who have excreted small amounts of 4-hydroxybutyric acid with normal SSADH activity. These patients must be followed to assess whether metabolite excretion persists. To avoid loss of 4-hydroxybutyric acid after routine acid extraction of urine, clinical laboratories should use extreme caution in removal of solvent. We have found it worthwhile to alkalize acidic extracts of urine to at least pH 5 after acid extraction to avoid substantial loss of 4-hydroxybutyric acid. Moreover, gas chromatographic analysis alone is insufficient to detect small elevations in urine; mass spectrometric analysis is essential for correct diagnosis. We and others use isotope-dilution methods for metabolite quantification in physiologic fluids from patients with 4-hydroxybutyric aciduria, which is the most accurate approach for quantitation.9

Several specialist laboratories have considerable expertise in accurately diagnosing SSADH deficiency through organic acid analysis. Our recommendation would be that accurate, quantitative, urine organic acid analysis be requested for any patient presenting with two or more features of mental, motor, or language delay and hypotonia of unknown cause. Such analyses are the only definitive way to diagnose SSADH deficiency; the diagnosis can be confirmed by determination of enzyme activity in white cells from whole blood. We think that increased use of organic acid analysis will lead to increased diagnosis of SSADH deficiency, which will result in a more accurate representation of the disease frequency. As additional patients are identified, we should have a better understanding of both the metabolic and clinical profile of SSADH deficiency.

ACKNOWLEDGMENTS

This work was supported in part by the Gamma Hydroxybutyrate Research Fund, Baylor University Medical Center and Baylor Health Care System, Dallas, TX. We are indebted to Rebecca Atnip for editing the manuscript, Dr G. Mues for assistance in translation of patient histories, and Dr M. I. Gibson for assistance in the construction of case reports, tabular formatting, and critical evaluation of the manuscript.

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