

# PEDIATRIC NEUROLOGY BRIEFS

## A MONTHLY JOURNAL REVIEW

J. GORDON MILLICHAP, M.D., F.R.C.P., EDITOR

Vol. 12, No. 8

August 1998

### METABOLIC DISORDERS

#### BIOTIN ENCEPHALOPATHY AND BASAL GANGLIA LESIONS

Ten patients with biotin-responsive basal ganglia disease are reported from the King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, and Brown University School of Medicine, Hasbro Children's and Rhode Island Hospitals, Providence, RI. All were of Middle Eastern, mainly Saudi ethnic origin, all were children of consanguineous marriages, and all had a history of siblings with a similar disease that was undiagnosed and resulted in death in 17 children. Patients diagnosed and treated were followed for 3 to 10 years. Symptoms of an acute or subacute encephalopathy, presenting between ages 1 and 14 years, usually pre-school, included a prodrome of confusion and lethargy followed by coma and vomiting, and progressing to dysarthria and dysphagia/drooling (8 patients), seizures (5), facial or gaze paralysis (4), dystonia and rigidity (10), opisthotonus (3), and quadriparesis (6). Following treatment with biotin, 5-10 mg/kg/day, symptoms resolved without neurologic sequelae. They returned when biotin was discontinued, sometimes resulting in residual paraparesis, dystonia, or mild mental retardation, despite reintroduction of biotin. The presumed defect in biotin metabolism or transporter mechanism was undetermined since enzyme assays for biotinidase and carboxylase, in addition to other biochemical, toxicological, and viral studies, were normal. Brain MRI always showed bilateral central necrosis of the head of the caudate nucleus and complete or partial involvement of the putamen, and lesions were unchanged after prolonged biotin therapy. (Ozand PT, Gascon GG, Essa MA et al. Biotin-responsive basal ganglia disease: a novel entity. *Brain* July 1998;121:1267-1279). (Respond: Pinar T Ozand MD, Department of Paediatrics, King Faisal Specialist Hospital and Research Centre, PO Box 3354, Riyadh 11211, Saudi Arabia).

COMMENT. A diagnosis of biotin-responsive basal ganglia syndrome should be considered in children born to consanguineous parents, and presenting as an acute or subacute encephalopathy, with confusion, vomiting and seizures, followed by symptoms of brainstem and extrapyramidal involvement, and accompanied by caudate and putamen necrosis on MRI. The first patient with this

---

PEDIATRIC NEUROLOGY BRIEFS (ISSN 1043-3155) © 1998 covers selected articles from the world literature and is published monthly. Send subscription requests (\$58 US; \$60 Canada; \$68 airmail outside N America) to **Pediatric Neurology Briefs - J. Gordon Millichap, M.D., F.R.C.P. - Editor**, P.O. Box 11391, Chicago, Illinois, 60611, USA.

The editor is Pediatric Neurologist at Children's Memorial Hospital and Northwestern University Medical School, Chicago, Illinois.

PNB is a continuing education service designed to expedite and facilitate review of current scientific information for physicians and other health professionals.

syndrome, diagnosed by Dr Edward Rabe, now of Maine, USA, had failed to respond to trials of acyclovir, thiamine, carnitine, phenobarbital and diazepam, but showed immediate improvement when biotin was introduced in megadoses, 10-40 x greater than those required in biotin deficiency states. Characteristic signs of the infantile type of biotin encephalopathy, including skin rash, alopecia, ketoacidosis, and organic acidemia, were absent, and presumably, the smaller biotin doses (5-10 mg daily) employed in cases of biotin deficiency were found ineffective. A defect in biotin transport across the blood-brain barrier was postulated, since assays of biotinidase and carboxylase were normal. See [Progress in Pediatric Neurology I, II, & III](#), (PNB Publishers) for reports of neonatal and infantile biotin encephalopathy. This apparent nonspecific effect of biotin in cases of idiopathic familial progressive encephalopathy might prompt trials of megadose biotin in children with chronic refractory encephalopathies.

### **PYRIDOXINE-DEPENDENT SEIZURES AND MRI CHANGES**

Longitudinal brain MRI findings in two patients presenting with neonatal, pyridoxine-dependent seizures and followed for 5 to 9 years are reported from the University of California, Davis, CA. Each patient had three serial MRIs, showing progressive dilation of ventricles and atrophy of cortex and white matter. Patient 1 with AED-resistant seizures was diagnosed at 3.5 months by IV 100 mg pyridoxine administration during EEG monitoring. Seizures characterized by lip smacking, tonic eye deviation, and limb jerking began 2 hours after birth and were initially responsive to phenobarbital. Treatment with 25 mg oral pyridoxine daily controlled seizures, but noncompliance resulted in prolonged seizures and severe developmental disability with hypotonia at 5 year follow-up. Patient 2 developed seizures consisting of eye deviation and facial twitching and responsive to phenobarbital at 4 days after birth. They recurred occasionally up to 8 months of age, when seizures became refractory to anticonvulsants and were found to respond to pyridoxine. During follow-up for 9 years, minor motor seizures, partial and generalized, occurred only during intercurrent illness or noncompliance with pyridoxine, 25 mg daily, treatment. Seizures were preceded by sleepiness and irritability. (Gospe SM Jr, Hecht ST. Longitudinal MRI findings in pyridoxine-dependent seizures. [Neurology](#) July 1998;51:74-78). (Reprints: Dr Sidney M Gospe Jr, Child Neurology, UC Davis Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817).

COMMENT. Pyridoxine-dependent seizures of neonatal onset and due to an inborn abnormality of GABA synthesis, if undiagnosed and untreated, can result in progressive cerebral atrophy and severe impairments of psychomotor development. Previous reports have emphasized that the control of seizures alone may not suffice in treating pyridoxine dependency. In order to prevent mental retardation and motor and language delay, it may be necessary to increase the dose of pyridoxine to 10 mg/kg/daily to normalize neurotoxic glutamate levels. Language and cognitive disabilities secondary to pyridoxine-dependency may be partially reversed using optimal pyridoxine dosage. (See [Progress in Pediatric Neurology III](#), PNB Publ, 1997;pp93-98).

### **GENE LOCATION FOR MOLYBDENUM COFACTOR DEFICIENCY**

Linkage of a molybdenum cofactor deficiency (MoCoD) gene to an 8-cM region on chromosome 6p21.3 has been localized by homozygosity mapping in 2 consanguineous affected kindreds of Israeli-Arab origin, including 5 patients, at the Department of Genetics, Tamkin Research Facility, Technion-Israel Institute of Technology, Haifa, Israel. These findings allow prenatal diagnosis with microsatellite markers and carrier detection of this fatal disorder. (Shalata A,