

# PEDIATRIC NEUROLOGY BRIEFS

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### METABOLIC AND HEREDO-DEGENERATIVE DISORDERS

#### NEUROPATHOLOGY OF GLUTARIC ACIDEMIA TYPE 1

The neuropathological findings in 5 children and 1 adult (8 months-40 years of age) with glutaric acidemia type 1 (GA-1), all N American aboriginals with the same homozygous mutation, were studied at the Manitoba Institute of Child Health, Winnipeg, and University of Western Ontario, London, Ontario, Canada; and University Children's Hospital, Heidelberg, Germany. Case 1, a male infant having 6 of 7 older siblings affected by GA-1, was jittery at birth, a seizure occurred at 3 months, and developmental delay, hypotonia and head bobbing were noted at 4 months. A CT at 6 months showed enlarged ventricles, wide frontal sulci, and fluid collections in the temporal fossae. He presented with vomiting, diarrhea, fever and dehydration at 8 months, becoming rapidly comatose. His head circumference was above the 99<sup>th</sup> percentile at birth and at 8 months. A repeat CT scan showed hemorrhage in the right temporoparietal region, and he died 3 days later. Autopsy revealed ischemic neuronal damage in the cerebrum and cerebellum, venous sinus thrombosis, dilated ventricles, and striatal, caudate and putamen atrophy, with neuron loss, astrocyte hypertrophy and microglial activation. Four of the 6 cases had macrocephaly, usually in infancy and at the time of the encephalopathic crises, all had striatal, caudate and putamen atrophy, and all brain regions demonstrated elevated GA and 3-OH-GA protein. The characteristic dystonia was reported in 3 patients. The neuropathological findings were similar to those described previously in 10 autopsied cases of other ethnic backgrounds. The role of organic acids as toxic and osmotic agents, and of dietary treatment of presymptomatic cases diagnosed by screening of populations at risk, is discussed. (Funk CBR, Prasad AN, Frosk P et al. Neuropathological, biochemical and molecular findings in a glutaric acidemia type 1 cohort. **Brain** April 2005;128:711-722). (Respond: Marc R Del Bigio MD PhD FRCP, Department of Pathology, University of Manitoba, D212-770 Bannatyne Avenue, Winnipeg MB, R3E 0W3, Canada).

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COMMENT. Glutaric acidemia type 1 (GA-1) is an autosomal recessive disorder of amino acid metabolism caused by a deficiency of glutaryl-CoA dehydrogenase, and leading to accumulation of glutaric acid, 3-OH-GA and glutaconic acid in blood, urine, CSF and brain tissue. Characteristic clinical features include macrocephaly at, or soon after, birth, an abrupt onset of dystonia between 6 and 18 months of age, often with a febrile illness, and death in early childhood. Caudate and putamen atrophy with neuronal loss are always present, and white matter spongiform degeneration is a frequent finding.

Strauss KA, in a Commentary (*Brain* 2005;128:697-699), stresses the clinician's dilemma in predicting when basal ganglia injury will occur (the progress of the disease can be variable), and the lack of effective therapy once the encephalopathy ensues. Plasma and urine organic acid measurements are unreliable in predicting the time of onset of neurologic symptoms. The Canadian report confirms previous findings that brain GA is very high in these patients, exceeding plasma and CSF levels two-fold, an accumulation caused either by a selective blood-brain-barrier affinity for GA or by an excess brain tissue production of GA, arising from the enzymatic block in degradation of lysine and tryptophan in the brain. The risk of brain injury in GA-1 may be inversely related to the efficiency of brain organic acid clearance. The commentary emphasizes the need to consider inter-organ transport mechanisms for GA and the prevention of striatal necrosis.

## **POLGI MUTATIONS IN INFANTILE HEPATOCEREBRAL SYNDROMES**

Nine patients, 2 sibling pairs and 5 singleton cases, with *POLGI* mutations associated with infantile fatal encephalopathy and hepatopathy, 8 having typical Alpers' syndrome (Alpers' hepatopathic poliodystrophy) and one a severe floppy infant syndrome with hepatic failure, are reported from the National Institute of Neurology, Milano; Meyer Children's Hospital, Florence; University of Verona; University Hospital, Monza, Italy; and University Children's Hospital, Hamburg, Germany. Patient 1, a boy, developed a torticollis after a few months of life and 2 episodes of sudden head drop at 10 months, followed by psychomotor arrest and regression, hypotonia, ataxia and myoclonus, first focal and later, generalized, with weakness requiring ventilatory assistance. Seizures were accompanied by a disorganized basal EEG pattern and multiple foci of paroxysmal activity. Brain MRI showed symmetrical lesions of basal ganglia, thalami, cerebellar dentate nuclei, and left occipital cortical and subcortical regions. MRS revealed an abnormal accumulation of lactic acid in the putamen and a reduction of the N-acetyl aspartate peak, an index of neuronal loss. Cholestatic jaundice, hypoglycemia and hypocoagulation followed and were accompanied by neurologic deterioration and death at 30 months of age. In two of the 8 patients with Alpers' syndrome, severe acute liver failure followed administration of valproate for control of myoclonus. Autopsy performed in 3 cases of Alpers' syndrome showed diffuse encephalomalacia and severe liver steatosis with lobular fibrosis and bile ductile proliferation. Analysis of *POLGI*, a major disease gene in mitochondrial disorders, revealed that all patients carried different allelic mutations, 2 nonsense and 7 missense changes, associated with a heterogeneous spectrum of clinical outcomes. (Ferrari G, Lamantea E, Donati A et al. Infantile hepatocerebral syndromes associated with mutations in the mitochondrial DNA polymerase- $\gamma$ . *Brain* April 2005;128:723-731). (Respond: Massimo Zeviani MD PhD, Unit of