PAROXYSMAL DISORDERS

GENE IDENTIFICATION IN ALTERNATING HEMIPLEGIA

Researchers at Georg Augustus University Gottingen, Germany studied the genetics of alternating hemiplegia of childhood (AHC) in 24 patients aged 8-35 years, using whole-exome sequencing to identify de novo mutations associated with the disease. ATP1A3 was the disease-associated gene. Three patients showed de novo missense mutations. The remaining 21 patients all showed disease-associated mutations in ATP1A3, including 6 de-novo missense mutations and 1 splice-site mutation. Comparing the genotypes and phenotypes of AHC patients with those of rapid-onset dystonia-parkinsonism, both disorders have ATP1A3 as the disease-associated gene, and overlapping clinical features include dystonic episodes triggered by emotional stress, a rostro-caudal involvement, and signs of brainstem dysfunction. AHC and rapid-onset dystonia-parkinsonism are allelic diseases related to mutations in ATP1A3 and form a phenotypical continuum of a dystonic movement disorder. (Rosewich H, Thiele H, Ohlenbusch A, et al. Heterozygous de-novo mutations in ATP1A3 in patients with alternating hemiplegia of childhood: a whole-exome sequencing gene-identification. **Lancet Neurol** 2012 Sep;11(9):764-73). (Response: Dr H Rosewich, Department of Paediatric Neurology, Georg August University Gottingen, Germany).

COMMENT. In a multi-author report from the Center for Human Genome Variation, Duke University School of Medicine, Durham, NC, exome sequencing of 7 patients with AHC and their unaffected parents identified de novo mutations in ATP1A3 in all 7. In a subsequent sequence analysis of ATP1A3 in 98 other patients with AHC, ATP1A3 mutations were identified in 74% cases. (Heinzen EL, et al. **Nat Genet** 2012 Jul 29;44(9):1030-4).

Evolution of hemiplegic attacks and epileptic seizures in AHC. (Saito Y et al. **Epilepsy Res** 2010 Aug;90(3):248-58). In 9 patients (4-40 years) with AHC, paroxysmal ocular movements and tonic, clonic, or myoclonic movements were the presenting symptoms (birth-8m). Ictal EEG of these episodes and associated hemiplegic episodes showed only generalized slow background activity. Epileptic seizures occurred at 2-16y in 7 patients: generalized tonic, clonic, myoclonic, tonic-clonic, or complex partial seizures. Ictal EEG in 4 patients recorded generalized sharp waves or polyspike-wave activities during clonic/myoclonic seizures. Patients with status epilepticus and psychomotor deterioration showed cerebellar atrophy and hippocampal changes on MRI.

METABOLIC DISORDERS

CEREBRAL FOLATE DEFICIENCY & RECEPTOR MUTATIONS

Researchers at University Medical Centre Gottingen, other centers in Germany, and Helsinki University Central Hospital, Finland screened 72 children with low 5-methyltetrahydrofolate (5-MTHF) concentrations in the CSF who developed neurological abnormalities after infancy. Ten individuals with developmental regression, ataxia,

cerebral hypomyelination, and cerebellar atrophy had nucleotide alterations in the folate receptor 1 gene, *FOLR1*. These included novel pathogenic alleles in 4, one splice mutation and 3 missense mutations, with absence of cellular binding of folic acid. The molecular studies did not consistently explain the phenotypic variations among patients with cerebral folate transport deficiency, and additional factors must be contributory. Most patients had frequent myoclonic seizures or infantile spasms and benefited from oral folinic acid. (Folic acid must be converted to biologically active 5-MTHF and folinic acid is preferred). Response occurred within 2 months with reduced frequency of seizures and improved motor skills. The EEG showed a slow background rhythm and multifocal epileptiform activity. MRI showed delayed or hypomyelination of cerebral white matter and cerebellar atrophy. (Grapp M, Just IA, Linnankivi T, et al. Molecular characterization of folate receptor 1 mutations delineates cerebral folate transport deficiency. **Brain** 2012 Jul;135(Pt 7):2022-31). (Respond: Dr Robert Steinfeld. E-mail: rsteinfeld@med.uni-goettingen.de).

COMMENT. Cerebral folate deficiency is a progressive neurologic disorder of childhood amenable to treatment with folinic acid. Mutations in the *FOLR1* gene are the most common and severe etiology of cerebral folate deficiency, and are associated with a characteristic phenotype with early onset (<3 years), developmental delay, ataxia, and seizures often resembling infantile spasms. Seizures may prove refractory to oral folinic acid, and parenteral or rarely intrathecal administration may be required. (McFarland R. Scientific commentaries. Cerebral folate deficiency – mishaps and misdirection. **Brain** 2012 Jul;135(Pt 7):2002-3).

EEG AND SEIZURE MANIFESTATIONS OF CEREBRAL FOLATE DEFICIENCY

Researchers from Duke University Medical Center, Durham, NC report the EEG and seizure manifestations in 2 patients with folate receptor autoimmune antibody-mediated primary cerebral folate deficiency. Case 1, a boy presented at age 6 months with flexion spasms of the trunk and extension of the arms occurring multiple times each day. The seizures were diagnosed as infantile spasms and the EEG showed hypsarrhythmia. Treatment with various anticonvulsant drugs and ACTH 80 U/m2 provided only minor seizure control. Decreased CSF 5-MTHF and elevated serum folate receptor antibodies discovered at age 3.25 years were consistent with an autoimmune etiology of cerebral folate deficiency. Treatment with folinic acid started at 1 mg/kg/day resulted in marked clinical and EEG improvement. MRI revealed diffuse brain volume loss. Case 2, a girl aged 4 years had a history of developmental delay and tonic seizures that increased in frequency after age 5 years. She had progressive regression with language deficits, hand wringing, and gait difficulty. Tests for Rett syndrome and related disorders were negative. With increasing age her seizures were multiple and refractory. The EEG showed subclinical electrical status epilepticus during sleep, covering >85% of the slow wave sleep background. Cerebral folate deficiency was identified at age 16 years, and seizure frequency and intensity improved with folinic acid initiated at a dosage of 0.5 mg/kg/day. The EEG showed less frequent multifocal spikes, and electrical status epilepticus during sleep resolved. (Steele SU, Cheah SM, Veerapandiyan A, Gallentine