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EPILEPTIC ENCEPHALOPATHIES

EARLY-ONSET EPILEPTIC ENCEPHALOPATHIES WITH STXBP1 MUTATIONS

Researchers at the Department of Molecular Genetics, University of Antwerp, and other centers in Belgium, The Netherlands, and Melbourne, Australia, analyzed the clinical phenotypes associated with STXBP1 mutations in a cohort of 106 patients with unexplained early-onset epileptic encephalopathies. Nine patients were diagnosed with Ohtahara syndrome, 32 had West syndrome, 14 had migrating partial seizures of infancy, and 2 patients had early myoclonic encephalopathy (EME). The term, early-onset epileptic encephalopathy (EOEE) was used for the remaining 49 patients with an undefined epileptic syndrome. Disease-causing mutations were indentified in six EOEE patients (5.7%). Age of seizure-onset ranged between 3 days and 4.5 months. None had Ohtahara syndrome, recently attributed to heterozygous mutation in STXBP1 gene, and 1 (3%) had West syndrome. In contrast, 5 (10.2%) of the patients with EOEE had STXBP1 mutations. The clinical phenotype of EOEE was a seizure onset at 3 days to 10 weeks, seizure type tonic, clonic, myoclonic, partial or epileptic spasms, psychomotor retardation, normal head growth, EEG at seizure onset showing focal or bilateral synchronous discharges, and hypsarrhythmia and West syndrome diagnosed in 3 patients by 5 month of age. Ataxia developed in 3, and 3 had profound retardation with hypotonia or dyskinetic movements. (Deprez L, Weckhuysen S, Holmgren P et al. Clinical spectrum of early-onset epileptic encephalopathies associated with STXBP1. **Neurology** Sept 28, 2010;75:1159-1165). (Response and reprints: Prof Dr P De Jonghe, MD, PhD, Neurogenetics Research Group, University of Antwerp, Belgium. E-mail: peter.dejonghe@ua.ac.be).

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COMMENT. Summarizing the phenotypic profile of infants with STXBP1 mutations: an early-onset epilepsy within the first 5 months of life, beginning as Ohtahara syndrome or as EOEE, frequent evolution to West syndrome, severe mental retardation, and neurologic deficits with dyskinesia.

Mutations in STXBP1 occur in patients with Ohtahara and West syndromes and are also present in 10% of patients with undefined early-onset epileptic encephalopathies without the burst-suppression EEG, typical of Ohtahara syndrome. The authors recommend STXBP1 mutation analysis in the evaluation of infants with unexplained EOEE. Other known genes for epileptic encephalopathies include SCN1A, ARX, CDKL5, and PCDH19. Neurodegeneration and mental retardation associated with STXBP1 are presumed to be an intrinsic property of the gene mutations, and are independent of the severity of the epilepsy and response to antiepileptic drugs.

Genetic causes of epileptic syndromes will be added to the clinical and EEG classifications of the epilepsies as a result of expanding molecular research. Holland KD and Hallinan BE of Cincinnati, in an editorial (**Neurology** 2010;75:1132-1133), recommend genetic testing for infants with unexplained epileptic encephalopathies. A gene mutation diagnosis may obviate the necessity for exhaustive and invasive investigations and lead to more effective therapy. Dravet syndrome, an encephalopathy caused by mutations in the SCN1A sodium channel gene, is exacerbated by sodium channel AEDs (eg carbamazepine) (reviewed by Millichap JJ et al. **Neurology** 2009;73:e59-62). Seizures caused by STXBP1 mutations respond to vigabatrin and are resistant to other AEDs. (Deprez L et al. 2010).

EARLY-ONSET EPILEPTIC ENCEPHALOPATHY WITH PHOSPHOLIPASE C BETA 1 DEFICIENCY

The clinical presentation and evolution of epileptic encephalopathy associated with a loss-of-function mutation in the phospholipase C-b 1 gene are reported in a male infant with infantile spasms treated at the University of Birmingham School of Medicine, UK. The infant's parents were consanguineous. He presented with eye rolling, lip smacking, tonic stiffening and flexion seizures at 10 weeks, and subsequently developed infantile spasms and hypsarrhythmia at 8 months of age, associated with severe neurological regression (West syndrome). Spasms were refractory to a 2-week course of vigabatrin but were controlled with a course of prednisolone (ACTH was declined). At 10 months he developed tonic-clonic seizures resistant to AEDs and at 13 months, the EEG showed generalized slowing, consistent with diffuse encephalopathy. MRIs at ages 5 and 13 months were normal. His head circumference was at the 0.4th centile at birth and at 2.5 years, when he was functioning at 0-3 month level and was unable to lift his head when prone or roll over. At 2.9 years he had spastic quadriparesis, he contracted adenovirus pneumonitis and died of respiratory failure. Post-mortem was not performed. Molecular genetic analysis of the index case revealed a homozygous deletion on chromosome 20 involving the phospholipase PLCB1 gene. Linkage to the phospholipase C-b 1 locus was absent in 12 other consanguineous families of children with infantile spasms. The findings were consistent with genetic heterogeneity in infantile spasms. This is the first loss of function PLCB1 mutation described in humans. (Kurian MA, Meyer E, Vassallo G, et al. Phospholipase C beta 1 deficiency is associated with early-onset epileptic