# PEDIATRIC NEUROLOGY BRIEFS A MONTHLY JOURNAL REVIEW

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

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## SEIZURE DISORDERS

### A NEW GENETIC MARKER FOR FEBRILE SEIZURES

Linkage analysis genetic studies were conducted in a four-generation Utah family with 21 members affected by febrile seizures inherited as an autosomal dominant trait, and results are reported from the University of Utah, Salt Lake City, UT. Seizures associated with fever were generalized tonic-clonic in pattern and they began between ages 5 months and 3 years (mean age, 1.3 years). Febrile seizures were recurrent in 18 patients, some having as many as 16 episodes, but none received antiepileptic medications and none had recurrences beyond 6 years of age (mean age, 4.1 years). Afebrile seizures of various types (generalized tonic-clonic, tonic, atonic, simple or complex partial seizures) occurred in 8 patients between ages 5 and 13 years, and electroencephalograms were abnormal in 5.

Eighteen chromosomal regions known to harbor epilepsy gene/loci tested negative for linkage to febrile seizures. These included loci (8g13-21, 19p, and 19q) previously showing linkage to familial febrile seizures. Subsequent to candidate gene testing, a genome-wide scan uncovered only one (D2S1245 on chromosome 2q) of 191 markers with a positive LOD score greater than 1.00. Genotypes collected on all family members, and fine mapping linkage using 13 markers within the D2S1245 and D2S277 interval, revealed LOD scores greater than 3.0 in 10 of the markers, and a maximum 8.08 LOD score with marker D2S2330. A critical 10-cM region of no recombination was defined by haplotype analysis between two flanking markers (D2S141 and D2S2345) on chromosome 2q23-24, which contained the FEB3 locus. The disease haplotype cosegregates in all 21 affected subjects, and the observed penetrance of the FEB3 disease locus in this family (97.5%) is considerably higher than that reported in other febrile seizure families (60-80%). (Peiffer A, Thompson J, Charlier C et al. A locus for febrile seizures (FEB3) maps to chromosome 2a23-24. Ann Neurol October 1999:46:671-678). (Respond: Dr Mark Leppert, University of Utah, Department of Human Genetics, 15 N 2030 E. Rm 7160. Salt Lake City, UT 84112).

COMMENT. In this expedited report, the authors have demonstrated, within a

PEDIATRIC NEUROLOGY BRIEFS (ISSN 1043-3155) © 1999 covers selected articles from the world literature and is published monthly. Send subscription requests (SS8 US; S60 Canada; S68 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. Fax: 312-943-0123. Visit our web site: www.pnbpublishers.com large, four-generation Utah family, significant evidence for a novel febrile seizure locus (FEB3) on chromosome 2q23-24 with linkage to the marker D2S2330. Four loci associated with a febrile seizure phenotype have now been defined, FEB1-3 and GEFS. The clinical variations observed in febrile seizure families can now be explained by genetic heterogeneity, as previously suspected, and ongoing genotype/phenotype correlations should segregate these febrile seizure genes and their specific mutations, leading to advances in their causes and treatment.

That the cause of febrile seizures and epilepsy is multifactorial has been expressed in numerous earlier reports (Millichap JG. Febrile Convulsions, Macmillan, 1968), but until recently the inheritance factor has not been supported by specific gene linkages. Evidence that febrile seizures have a strong genetic component has been derived from family and twin studies (Lennox WG and Lennox MA. Epilepsy and Related Disorders, Little, Brown, 1960), and EEG studies (Stores G. Arch Dis Child 1991;66:554-557). See Progress in Pediatric Neurology II, PNB Publ, 1994;pp20-22, for literature abstracts and commentaries.

An excess of concordant monozygotic compared to dizygotic twin pairs, observed for both febrile seizures and epilepsy, is significant, showing a factor of almost 3 to 1. The familial incidence of febrile seizures is quoted as high as 58%, with a mean of 17%; the incidence was 30% in an unselected series of patients. Siblings of affected children have a 10% risk of developing febrile seizures. If the index child and 1 parent are affected, the risks to siblings are 30-40% (50% if both parents are affected). The risk for developing afebrile seizures and epilepsy in later life is estimated at 2% to 7% of children with simple febrile seizures, but the risk is higher in those with complex febrile seizures. In the Utah febrile seizure family and FEB3 gene carriers, all having simple febrile seizures, the risk of epilepsy was 47%, and considerably higher than that reported in population studies and most febrile seizure family (Nelson KB, Ellenberg JH. Eds Febrile Seizures. New York, Raven Press, 1981). This indicates an unusually high epilepsy predisposition among the FEB3 family members, and the likelihood of an additional predisposing epilepsy gene.

#### MEG LOCALIZATION IN EPILEPSY SURGERY

The concordance rate between the anatomical location of interictal magnetoencephalography (MEG) spike foci with the location of ictal onset zones identified by invasive ictal intracranial electroencephalographic (EEG) recordings was determined in 11 children evaluated for epilepsy surgery at the Hospital for Sick Children and University of Toronto, Ontario, Canada. In 10 of 11 patients, the anatomical location of epileptiform discharges determined by MEG corresponded to the ictal onset zone recorded by subdural electrodes. Functional EEG mapping of the somatosensory hand area was the same as the MEG localization. Seizures were completely or more than 90% controlled after surgery in 9 patients, at a mean follow-up of 24 months. Noninvasive magnetic source imaging by MEG and MRI provides an accurate presurgical localization of epileptic foci in children with refractory nonlesional extratemporal epilepsy and may obviate the need for invasive monitoring. (Minassian BA, Otsubo H, Weiss S, Elliott I, Rutka JT, Snead III, OC. Magnetoencephalographic localization in pediatric epilepsy surgery: Comparison with invasive intracranial electroencephalography. Ann Neurol October 1999;46:627-633). (Respond: Dr O Carter Snead III, Division of Neurology, Department of Paediatrics, Hospital for Sick Children and University of Toronto, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8).

COMMENT. MEG detects magnetic fields generated by intraneuronal electrical currents, and MEG spikes correlate precisely with irritative zones