

Phoenix, AZ 85013. E-mail: [harold.rekate@bnaneuro.net](mailto:harold.rekate@bnaneuro.net)).

COMMENT. The cause of headache in shunted hydrocephalus is often not identified with a CT scan. Headache relieved by lying down may point to over-drainage of CSF, intracranial hypotension and slit ventricle syndrome. Headache exacerbated by exercise points to an intermittent obstruction of CSF flow. If the ventricles do not expand with shunt failure, a normal volume hydrocephalus with increased ICP is suspected. All require immediate neurosurgical intervention. Seizures are an additional complication of slit ventricle syndrome. The development of spike and sharp wave EEG abnormality following a shunting operation for hydrocephalus may indicate shunt malfunction and over-drainage of CSF. (Saukkonen A et al. *Child's Nerv Syst* 1988;4:344-347; *Ped Neur Briefs* May 1989).

## SEIZURE DISORDERS

### GENETICS OF FEBRILE SEIZURES AND EPILEPSY (GEFS+)

Mutations in 3 genes *SCN1A*, *SCN1B* and *GABRG2* have been shown to cause GEFS+ in families of various ethnic origins. The occurrence of mutations in these genes in 19 families of Scandinavian origin with a history of GEFS+ was studied at Ulleval University Hospital, Oslo, Norway, and centers in Denmark. Families were identified from population-based twin registries in Denmark and Norway. One mutation in *SCN1A* was identified in a Danish family with phenotypes consistent with GEFS+. The mutation was not found in healthy and unrelated controls. No mutations were found in any of the other families. (Selmer KK, Egeland T, Solaas MH et al. Genetic screening of Scandinavian families with febrile seizures and epilepsy or GEFS+. *Acta Neurol Scand* April 2008;117:289-292). (Respond: Dr Keja K Selmer, Ulleval University Hospital, Kirkeveien 166, 0407 Oslo, Norway).

COMMENT. GEFS+ is an autosomal dominant disorder characterized by multiple febrile seizures persisting beyond age 5 years and complicated by afebrile seizures of absence, myoclonic or atonic types. Seizures cease in mid-childhood. (Scheffer IE et al. *Brain* 1997;120:479-490; Idem. *Epilepsia* 2005;46:41-47). Genes on chromosomes 2q24 and 19q13 encode subunits of the voltage-gated sodium ion channels, while the gene on 5q31 codes for the  $\gamma$ -subunit of the  $\gamma$ -aminobutyric acid (GABA) receptor. The genes responsible for GEFS+ show considerable heterogeneity and variable expressivity. GEFS+ is an evolving composite of many syndromes, with shared genetic susceptibility. (Nordli DR Jr. *Epilepsia* 2005;46(Suppl 9):48-56). While the definition of GEFS+ is continually changing and probably involves many genes, the common denominator is the association with febrile seizures.

**Failure of replication of epilepsy gene associations** is discussed by researchers from Columbia University Medical Center, and New York State Psychiatric Institute, New York, NY. (Pal DK, Strug LJ, Greenberg DA. *Epilepsia* 2008;49:386-392). Over 50 genetic associations with various idiopathic epilepsy syndromes are reported but most have not been replicated. Genetic heterogeneity is a confounder in population-based studies, in both

association and linkage studies. Linkage, association, and mutation analyses are the most common methods of evaluating candidate genes in epilepsy. The authors advocate the integration of results from different experimental methods rather than insisting only on replication.

Discovery of susceptibility genes and their association with drug responsiveness and side-effects should permit new diagnostic and therapeutic options in the management of the epilepsies. (Helbig I, Scheffer IE, Mulley JC, Berkovic SF. Navigating the channels and beyond: unravelling the genetics of the epilepsies. **Lancet Neurol** March 2008;7:231-245).

## COGNITIVE IMPAIRMENT IN TUBEROUS SCLEROSIS COMPLEX

Seizure histories, EEG recordings and intelligence equivalents and their relation to tuber/brain proportion (TBP) measured by 3 dimensional MRI were evaluated in 61 patients with tuberous sclerosis complex (TSC), in a study at University Medical Center, Utrecht, the Netherlands. Mean age at examination was 17.9 (range 1.6 to 59) years, with 20% of patients age 5 years or less. Diagnosis was confirmed by mutation analysis in 44 (TSC1 mutation in 14 and TSC2 mutation in 30 patients). Seizures occurred in 51 (85%) patients, including infantile spasms in 21 (40%). Age at seizure onset was 1 day to 37 years (mean 2.2 years). EEG epileptiform activity in 46 (79%) patients was unifocal in 16 and multifocal in 30. Tubers detected in all patients numbered from 7 to 58 (mean 28). The mean TBP was 1.3% (range 0.2-5.1%). Intelligence equivalent (IE) ranged from 7-119 (mean 69). IE was below average (<90) in 48 (81%) patients and severely below average (<70) in 33 (56%). Cognition index was a mean of 1.7 (range 1.0-3.7) and was below average in 46 (78%) patients.

Number of tubers was not related to age at seizure onset, infantile spasms, or cognitive function. In contrast, TBP was inversely related to age at seizure onset and cognitive function. Patients with a below average IE had a TBP >1%, and those with above average IE had a TBP <1%. Patients with epilepsy had a lower IE than those without epilepsy. Earlier seizure onset, infantile spasms, and a TSC2 mutation were associated with a lower IE and lower cognition index. (Jansen FE, Vincken KL, Algra A et al. Cognitive impairment in tuberous sclerosis complex is a multifactorial condition. **Neurology** March 2008;70:916-923). (Reprints: Dr FE Jansen, Department of Neurology, C03236, University Medical Centre, PO Box 85500 GA Utrecht, the Netherlands). E-mail: [f.e.jansen@umcutrecht.nl](mailto:f.e.jansen@umcutrecht.nl)

COMMENT. The incidence of seizures and below average intelligence in patients with tuberous sclerosis is 85 and 81%, respectively. Mental retardation (IQ <70) occurs in approximately 50%. Patients with TSC2 mutation are younger at seizure onset, are more cognitively impaired, have more tubers, and have a greater TBP. The proportion of the total brain volume occupied by tubers (TBP) in patients with tuberous sclerosis is a better predictor of cognitive function than tuber number. Age at seizure onset is an independent determinant of cognitive function. The findings point to the importance of aggressive therapy and early seizure control in the management of tuberous sclerosis complex complicated by infantile spasms. Patients with infantile spasms generally have better outlook when treated early. ACTH has a beneficial response in 80% of patients less than one year of age and in 22% when diagnosis and treatment are delayed after one year. (Millichap JG, Bickford RG.