

## SEIZURE DISORDERS

### **VALPROATE AND RISK OF FRACTURE IN RETT SYNDROME**

The association between fracture risk and commonly used antiepileptic drugs (AEDs) in 233 cases of Rett syndrome was investigated by researchers at medical centers in Australia. Patients were sourced from the population-based Australian Rett Syndrome Database. After controlling for mobility, epilepsy diagnosis and genotype, use of valproate (n=134, mean age 15.8 years), prescribed alone or with other AEDs, increased the risk of fracture threefold after at least 1 year and after 2 or more years. Lamotrigine (n=100) caused a lesser increase in risk in the first year of use but no increase in subsequent years. Carbamazepine (n=114) slightly decreased the risk of fracture after 2 or more years of use. These effects were present when analyses were repeated using only cases of Rett syndrome with X-linked MECP2 mutations (n=183), with results similar to all cases, including those clinically diagnosed. (Leonard H, Downs J, Jian L et al. Valproate and risk of fracture in Rett syndrome. *Arch Dis Child* June 2010;85:444-448). (Respond: Dr Helen Leonard, Telethon Institute for Child Health Research, University of Western Australia, PO Box 855, West Perth 6872, Western Australia. E-mail: [hleonard@icmr.uwa.edu.au](mailto:hleonard@icmr.uwa.edu.au)).

COMMENT. Rett syndrome is associated with reduced mineral density and a fracture rate, mostly affecting the femur, nearly 4 times that of the general population. Seizures occur in 80% of girls and women with Rett syndrome, and epilepsy increases risk of fracture, especially when treated with valproate for 1 year or longer. Risk is not increased by other AEDs and may be reduced by carbamazepine. Long-term treatment of epilepsy in Rett syndrome patients should favor AEDs other than valproate when possible.

Researchers at Royal Melbourne Hospital and Universities of Melbourne and New South Wales, Australia, have characterized adverse effects of valproate on bone mineralization of various strains of mice identified as either sensitive or resistant. (Senn SM et al. *Epilepsia* June 2010;51:984-993). Bone mineral content was reduced 9.1% and trabecular volumetric density by 10.7% following chronic valproate treatment in mice strains sensitive to AED-induced bone loss. Resistant strains showed no adverse effects of valproate on bone. The strain-specific effects suggest a role of genetic factors in the pathogenesis of AED-induced bone disease.

### **LONG-TERM FOLLOW-UP OF DRAVET SYNDROME TO ADULTHOOD**

Researchers at Department of Child Neurology, Okayama University Hospital, Japan, have followed 31 patients with Dravet syndrome (DS) (14 typical and 17 borderline DS) from childhood to at least 18 years of age. The study began with 37 patients but 6 (16.2%) died in childhood (5–12 years), 3 in status epilepticus. Clinical findings in the 31 typical and borderline cases became largely similar in adolescence and adulthood. Seizures were intractable in childhood, but suppressed in five (16.1%) during

follow-up. Seizures considered generalized convulsive initially in 40 children, when captured by ictal EEG at 7 years of age, were of focal origin in 35 (87.5%). Myoclonic, atypical absence, and photo- and pattern-sensitive seizures disappeared by 20 years of age in most typical cases. Patients with <3 episodes of convulsive status epilepticus in childhood and no EEG spikes on follow-up ( $P<0.001$ ) had a seizure-free outcome as adults ( $P=0.018$ ). Seizure freedom was not correlated with SCN1A mutation type, gender, type of DS, or generalized spike-waves on EEG. Of 26 (83.9%) patients with persisting seizures as adults, 19 (73%) had mostly nocturnal seizures; 10 (38.5%) continued to have seizures provoked by fever, none with status epilepticus. At last follow-up, seizures were refractory in 84%, and 5 patients (16.1%) had 10-29 seizures per month. Seven patients (22.6%) spoke no words and 9 (29%) spoke only several words. Five (16.1%) made simple conversation and could read a little. Occipital alpha rhythms in follow-up EEGs at a mean age of 23.8 years correlated with less severe intellectual disability ( $P=0.002$ ). Prevention of occurrence of convulsive status epilepticus in childhood was critically important for improved seizure outcome in DS in adulthood. (Akiyama M, Kobayashi K, Yoshinaga H, Ohtsuka Y. A long-term follow-up study of Dravet syndrome up to adulthood. *Epilepsia* June 2010;51:1043-1052). (Respond: Dr K Kobayashi, Department of Child Neurology, Okayama University Hospital, Shikatacho 2-chome 5-1, Kitaku, Okayama, Japan 700-8558. E-mail: [k\\_koba@md.okayama-u.ac.jp](mailto:k_koba@md.okayama-u.ac.jp)).

COMMENT. In this long-term, follow-up study of patients diagnosed with Dravet syndrome, the main factor associated with improvement of seizure prognosis is the prevention of occurrence of convulsive status epilepticus in childhood. Details of treatment were not listed, except that the approval and introduction of topiramate in 2007 controlled seizures in 4 previously unresponsive patients.

## EFFECTS OF DTP VACCINATION ON RAVET SYNDROME

An association between DTP vaccination and onset of seizures in 40 patients diagnosed with Dravet syndrome was investigated by retrospective analysis of medical and vaccination records at Heidelberg Hospital, Victoria, Australia. Patients with mutations in SCN1A whose first seizure was a convulsion were separated into 2 groups, those whose first seizure occurred on the day of or day after vaccination ( $n=12$ ) (the vaccination-proximate group), and those with seizure onset 2 days or more after vaccination ( $n=25$ ) or before vaccination ( $n=3$ ) (the vaccination-distant group). Mean age at seizure onset was 18.4 weeks (SD 5.9) in the vaccination-proximate group and 26.2 weeks (SD 8.1) in the vaccination-distant group (difference  $p=0.004$ ). Intellectual outcome, subsequent seizure type, and mutation type were similar in the two groups ( $p$  values  $>0.3$ ). Intellectual outcome did not differ between patients who received vaccinations after seizure onset and those who did not. Vaccination might trigger earlier onset of seizures in children with SCN1A mutations and susceptibility to Dravet syndrome, but, by post-hoc analysis of data, vaccinations before or after onset of Dravet syndrome do not affect intellectual outcome. (McIntosh AM, McMahon J, Dibbens LM et al. Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study. *Lancet Neurol* June 2010;9:592-598). (Respond: Prof Samuel F Berkovic. E-mail: [s.berkovic@unimelb.edu.au](mailto:s.berkovic@unimelb.edu.au)).