nervous system. In Pediatric Neurology, Ed. Millichap JG. **Ped Clin N Amer** 1967;14:865-880).

RATE OF DEVELOPMENT OF INTRACTABLE EPILEPSY

The time taken to develop intractability of epilepsy was determined prospectively in a cohort of 613 children followed in the Connecticut Study for a median of 9.7 years and reported by researchers from Northern Illinois University, DeKalb, IL; University of California Los Angeles, CA; Yale Medical School, New Haven, CT; and Albert Einstein College of Medicine, Bronx, NY. Intractability was defined in two ways: 1) 2 drugs failed, 1 seizure/month (average) for 18 months (stringent definition), and 2) failure of 2 drugs. Delayed intractability was defined as 3 or more years after epilepsy diagnosis. Intractability (stringent form) developed in 83 children (13.8%), and the 2-drug definition of intractability was met by 142 (23.2%). Intractability was delayed in 26 (31.3%) children meeting stringent and in 39 (27.5%) meeting the 2-drug definition. Intractability varied with the epilepsy syndrome and was delayed more often in focal than catastrophic (including encephalopathic) epilepsies (stringent: 46.2 vs 14.3%, p=0.003; 2-drug: 40.3 vs 2.2%, p<0.0001). Early remission preceded delayed intractability in 65.4 to 74.3% of cases. After developing intractability, 20.5% entered remission, and 13.3% were seizure-free at last follow-up. Referral to surgery may be delayed for 20 or more years, because of this interim period of remission. (Berg AT, Vickrey BG, Testa FM, et al. How long does it take for epilepsy to become intractable? A prospective investigation. **Ann Neurol** June 2006;60:73-79). (Respond: Anne T Berg PhD, Department of Biology, NIU, DeKalb, IL 60115).

COMMENT. In the earlier Dutch study of 453 children with newly diagnosed epilepsy followed prospectively for 5 years (Arts WFM et al. **Brain** 2004;127:1774-1784), significant variables for the worst outcome group included a symptomatic or cryptogenic etiology, early age at onset, and a history of febrile seizures. Of 108 (24%) patients with a terminal remission (TS) of <1 year, 27 had intractable seizures at 5 years. Of patients receiving 2 or more AEDs, almost 60% had a TR5 >1 year. AEDs were successfully withdrawn in 227 (59%). The course of epilepsy was constantly favorable in 51%, steadily poor in 17%, remitting after intractability in 25%, and deteriorating in 6% (**Ped Neur Briefs** August 2004;18:57-59).

VALPROATE-INDUCED HYPERAMMONEMIC ENCEPHALOPATHY

Valproate-induced hyperammonemic encephalopathy (VHE), predisposing causes, clinical, laboratory, and EEG findings, and therapy are reviewed from the Hospital del Mar, Barcelona, Spain. Urea cycle enzyme deficiency, especially ornithine transcarbamylase (OTC), is an inherited cause of hyperammonemia and a risk factor for developing VHE in patients taking VPA. Screening tests are recommended in patients with a known family history of OTC deficiency, and in patients who develop unexplained episodes of confusion, lethargy, and vomiting, and/or increased frequency of seizures, while on VPA therapy. Blood ammonia level, renal and liver function, and urinary orotic acid excretion should be tested. Blood VPA levels are within therapeutic ranges in most cases of VHE, and the dose of VPA and the height of the ammonia level are not related to VHE severity. Organic acidemias

should be suspected when hyperammonemia is associated with acidosis, ketosis, and low bicarbonate level. Topiramate and phenobarbital favor hyperammonemia, because of inhibition of cerebral glutamine synthetase; topiramate also inhibits carbonic anhydrase, leading to hyperammonemia by affecting the urea cycle. Polytherapy, including topiramate, phenobarbital, phenytoin and carbamazepine, should be avoided with VPA. Hyperammonemia leads to an increase in cerebral glutamine, which produces astrocyte swelling and cerebral edema. The EEG shows continuous generalized slowing, a predominance of theta and delta activity, occasional bursts of frontal rhythmic delta, and triphasic waves. Prompt diagnosis and treatment with supplements of carnitine can lead to a favorable response. (Segura-Bruna N, Rodriguez-Campello A, Puente V, Roquer J. Valproate-induced hyperammonemic encephalopathy. **Acta Neurol Scand** July 2006;114:1-7). (Respond: Dr Nuria Segura-Bruna, Servei de Neurologia, Hospital del Mar, Passeig Maritim, 25-29, 08003, Barcelona, Spain).

COMMENT. In contrast to the above report and others, Beghi E et al (**Epilepsia** 1990;31:346-352) found a significant correlation between serum ammonia level and VPA dosage. A review of 132 fatal cases of valproate hepatotoxicity worldwide found that 65% were developmentally delayed, 75% were taking additional AEDs, and 65% were below 2 years of age (Konig St A, et al. **Epilepsia** 1994;35:1005-1015). In a report of 29 valproate case fatalities in the US between 1986 and 1996, risk factors also included young age (1:600 risk <2 years), and coincident metabolic disorders (Alpers' disease). (Bryant AE III, Dreifuss FE. **Neurology** 1996;46:465-469). Metabolic testing is recommended in young children (<2 years) with developmental abnormalities before prescribing VPA.

A review of the role of valproate therapy in the treatment of pediatric epilepsy emphasizes its superior efficacy and minimizes its toxicity (Aldenkamp A et al. **Acta Neurol Scand** August 2006;114 (Suppl 184):1-13). Given the number of fatalities reported in the past two decades, the potential adverse effects of valproate deserve at least equal attention and caution. The risks of valproate in the prophylaxis of febrile seizures, for example, outweigh the benefits (Wheless JW et al. **J Child Neurol** 2005;20(Suppl 1);S34-S35), and in pediatric epilepsy, careful monitoring is mandatory. The FDA-approved indications for valproate are complex partial seizures + other seizure types and simple and complex absence seizures (as monotherapy or adjunctive therapy); mania in adults; and migraine prophylaxis in adults (Golden AS, Haut SR, Moshe SL. Nonepileptic uses of antiepileptic drugs in children and adolescents. **Pediatr Neurol** June 2006;34:421-432).

ATTENTION DEFICIT DISORDERS

RESPONSE OF ADHD WITH GIANT SEP TO VALPROATE

Three boys, ages 4.5, 6, and 6.7 years, with attention deficit/hyperactivity disorder (ADHD) associated with giant somatosensory evoked potentials (SEP), who responded well to extended-release valproate (ER-VPA), are reported from the University of Tokushima Graduate, and Miyoshi Medical Clinic, Higashikagawa, Japan. Of 20 children with ADHD, 17 boys and 3 girls, ages 3 to 13 years, 6 showed giant SEPs, defined as peak-peak amplitude of N20-P25 that exceeded 10mcV, on median nerve stimulation. Three also had Tourette's