

HALLUCINATIONS AFTER VALPROIC ACID WITHDRAWAL

Child psychiatrists and neurologists in Utrecht, The Netherlands report case histories of 2 girls, ages 4 and 12 years, with a history of epilepsy who developed hallucinations after withdrawal of valproic acid (VPA). The 4-year-old woke up at night and complained of seeing and hearing snakes in her bed, and the 12-year-old heard voices and saw nonexistent persons. When VPA was restarted the hallucinations rapidly disappeared. The hallucinations were explained by enhancement of dopaminergic neurotransmission elicited by a decrease of GABA or rebound of glutaminergic activity after rapid withdrawal of VPA. A possible role of VPA in controlling a predisposition to hallucinations is suggested. (de Laat SAA, Hillegers MHJ, Jansen FE, Braun KP, de Graeff-Meeder ER. Hallucinations after withdrawal of valproic acid. *Pediatrics* 2012 Jul;130(1):e236-8). (Respond: Elizabeth R de Graeff-Meeder, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands. E-mail: b.degraeff@umcutrecht.nl).

COMMENT. The antiepileptic activity of VPA has several proposed mechanisms, including the enhancement of GABA. Increased dopamine release due to decreased GABA activity is suggested as a cause of hallucinations after VPA withdrawal.

FENFLURAMINE ADD-ON THERAPY OF DRAVET SYNDROME

Researchers at Antwerp University Hospital and University of Leuven, Belgium report 12 patients, 7 female and 5 male, age range 3-35 years, with a genetically proven diagnosis of Dravet syndrome who received fenfluramine (mean dose 0.34 (0.12-0.90) mg/kg/day) as add-on therapy. Seven (58%) patients had been seizure free for a mean of 6 (1-19) years. When fenfluramine treatment was discontinued in 7 patients, seizures recurred in 3; seizures were controlled when fenfluramine was reintroduced. Two patients developed a mild thickening of one or two cardiac valves without clinical symptoms. (Ceulemans B, Boel M, Leyssens K, et al. Successful use of fenfluramine as an add-on treatment for Dravet syndrome. *Epilepsia* 2012 Jul;53(7):1131-9). (Respond: Berten Ceulemans MD, PhD, Department of Neurology-Pediatric Neurology, Antwerp University Hospital, Wilrijkstraat 10, B 2650 Edegem, Belgium. E-mail: berten.ceulemans@uza.be).

COMMENT. Fenfluramine is a substituted phenylethylamine structurally related to amphetamine. The combination “Fen-Phen” anti-obesity product was withdrawn from the market in the US in 1997 because of serious cardiac side effects. The effectiveness of fenfluramine in treatment of self-induced photosensitive epilepsy was reported in 1985 (Aicardi J, Gastaut H. *N Engl J Med* 1985 Nov 28;313(22):1419) and confirmed in 1996 (Boel M, Casaer P. *Neuropediatrics* 1996 Aug;27(4):171-3).

The use of stimulants in the treatment of epilepsy is not new. In 1942, Cook and Dole report the effectiveness of dl-amphetamine (Benzedrine) (Cook GH, Dole JA. *Dis Nerv Syst* 1942 Nov;3:366-370), and in 1955, the classic, Goodman and Gilman textbook includes reference to the control of “petit mal” and the associated EEG spike and wave discharges following d-amphetamine (Dexedrine). (Goodman LS, Gilman A. *The Pharmacological Basis of Therapeutics*. 2nd Ed, New York, Macmillan, 1955).

In 1972, Livingston summarized the literature on the effectiveness of d-amphetamine in the control of “petit mal” and other epilepsies. For children <6 years old, Livingston recommended initial d-amphetamine doses of 2.5 mg daily, and >6 years, 2.5 mg 2 x daily (Livingston S. **Comprehensive Management of Epilepsy in Infancy, Childhood and Adolescence**. Springfield, IL, Charles C Thomas, 1972, pp. 198 and 298-300). Given the adverse publicity associated with fenfluramine, future trials of stimulants in Dravet syndrome patients might substitute d-amphetamine (l-amphetamine is found ineffective as an anticonvulsant). For the early recognition and when to suspect the diagnosis of Dravet syndrome, see a review from the Comprehensive Epilepsy Center, Ann & Robert H. Lurie Children’s Hospital of Chicago (Millichap JJ, Koh S, Laux LC, Nordli DR Jr. **Neurology** 2009 Sep 29;73(13):e59-62).

METABOLIC DISORDERS

GABA-ERGIC DYSFUNCTION IN SUCCINIC SEMIALDEHYDE DEHYDROGENASE DEFICIENCY

Investigators at the Clinical Epilepsy and Neurorehabilitation Sections, NIH, Bethesda, MD; Albert Ludwigs University, Freiberg, Germany; and Children’s National Medical Center, Washington, DC used transcranial magnetic stimulation (TMS) to quantify the excitation and inhibition in primary motor cortex in 8 patients (mean age 15.4 years) with succinic semialdehyde dehydrogenase (SSADH) deficiency. All patients were severely affected and many showed symptoms of ADHD and anxiety. Long interval intracortical inhibition was significantly reduced and the cortical silent period was significantly shortened in patients with SSADH deficiency compared to heterozygous parents and controls. Long interval intracortical inhibition and cortical silent period are thought to reflect GABA receptor-mediated inhibitory circuits, pointing to a GABA-ergic motor cortex dysfunction in patients with SSADH deficiency. (Reis J, Cohen LG, Pearl PL, et al. GABA-ergic motor cortex dysfunction in SSADH deficiency. **Neurology** 2012 Jul 3;79(1):47-54). (Response: Dr Reis. E-mail: janine.reis@uniklinik-freiburg.de).

COMMENT. SSADH deficiency is a rare autosomal recessive disorder of GABA degradation with elevation of gamma-hydroxybutyric acid and GABA. Infants present with developmental delay, hypotonia, retardation, ataxia, seizures, hyperkinetic behavior, aggression, and sleep disturbances. Urine organic acids show 4-hydroxybutyric/gamma-hydroxybutyric aciduria. MRI may show globus pallidus T2 abnormalities. TMS may be helpful in detection of homozygous carriers and in diagnosis of SSADH deficiency.

INFECTIOUS DISORDERS

RESIDENTS’ LUMBAR PUNCTURE SKILLS AFTER SIMULATION-BASED EDUCATION

Researchers in the Departments of Medicine and Neurology at Northwestern University Feinberg School of Medicine, Chicago, IL evaluated the effect of simulation-