

PEDIATRIC NEUROLOGY BRIEFS

A MONTHLY JOURNAL REVIEW

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

Vol. 12, No. 3

March 1998

SEIZURE DISORDERS

MECHANISM OF ANTICONVULSANT ACTION OF ACTH

The effects of adrenocorticotrophin hormone (ACTH) in 23 children with intractable epilepsies and its mechanism of action are reported from the Department of Paediatric Neurology, Royal Hospital for Sick Children, Edinburgh, UK. Patients ranged in age from 8 months to 9 years. The epileptic syndrome diagnoses were West syndrome in 5, Lennox-Gastaut in 7, Landau-Kleffner in 6, and unclassified in 4. The EEG showed generalized electrical status in 16 and focal status in 5. Initial treatment with diazepam (0.2 mg/kg) showed a positive electrophysiologic response in 17 patients, all of whom subsequently responded to ACTH. ACTH 0.5 mg daily for 2 weeks abolished seizures completely in 9 and reduced seizure frequency in 10. Epileptic discharges in the EEG were also abolished in 15 after ACTH. The mechanism of action proposed is independent of the effect on the adrenal, similar to that of benzodiazepines, not restricted to infantile spasms, and is probably related to the production of neurosteroids and extracellular adenosine in the brain, which modulate the GABA receptor. (O'Regan ME, Brown JK. Is ACTH a key to understanding anticonvulsant action? Dev Med Child Neurol February 1998;40:82-89). (Respond: Dr ME O'Regan, Department of Paediatric Neurology, Royal Hospital for Sick Children, Sciennes Road, Edinburgh, UK).

COMMENT. Evidence that ACTH may be effective in the treatment of intractable epilepsies of various patterns and syndromes, not restricted to infantile spasms, is further supported by this study. Antiepileptic effects in children with Lennox Gastaut and Landau Kleffner syndromes have been well documented in previous reports. ACTH effectiveness in children with status absence epilepsy and generalized tonic-clonic seizures refractory to AEDs has also been reported (Millichap JG. ACTH treatment of childhood refractory epilepsy. Neurology March 1991;41 (Suppl 1):201). Hypsarrhythmia is not a sine qua non for ACTH therapy. (Progress in Pediatric Neurology II, 1994:102).

ACTH and experimental seizures in adrenalectomized animals. Laboratory studies at the Division of Neurology, Children's Memorial Hospital,

PEDIATRIC NEUROLOGY BRIEFS (ISSN 1043-3155) © 1998 covers selected articles from the world literature and is published monthly. Send subscription requests (\$58 US; \$60 Canada; \$68 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.

Chicago, in 1965, demonstrated a *reduction* in the seizure threshold following adrenalectomy and in both intact and adrenalectomized young rats, following ACTH. Measurements of brain and plasma electrolytes showed that the reduced seizure threshold was correlated with an increase in the concentration of intracellular sodium in the brain. The ACTH effects on seizure threshold and brain sodium were independent of the adrenal. Animals with seizure thresholds experimentally lowered by methods other than adrenalectomy might demonstrate the anticonvulsant effect of ACTH observed clinically (Wasserman MJ, Belton NR, Millichap JG. Effect of corticotropin (ACTH) on experimental seizures. Adrenal independence and relation to intracellular brain sodium. Neurology Dec 1965;15:1136-1144).

NOCTURNAL FAMILIAL FRONTAL LOBE EPILEPSY

A clinical and video-polysomnographic (VPS) study in 40 patients complaining of repeated abnormal nocturnal motor and/or behavioral phenomena, from 30 unrelated Italian families, is reported from the Sleep Disorders Centre and the Department of Biology and Genetics for Medical Sciences, University of Milan, Italy. A diagnosis of autosomal dominant nocturnal frontal lobe epilepsy (ADFLE) was strongly suggested by electroclinical manifestations, which included nocturnal enuresis, violent behavior, and other features seen also in 'typical' parasomnias. The VPS recordings confirmed sudden awakenings and dystonic/dyskinetic movements in 42%, complex behaviors in 13%, and violent behavior in 5%. Ictal epileptiform abnormalities and rhythmic slow activity in frontal areas were recorded on the EEG in 32% and 47% of patients, respectively. A correct diagnosis of epilepsy had been made previously in only 18%, and >80% had been misdiagnosed as parasomnia. Seizures were controlled by antiepileptic drugs in 73%. Pedigree analysis on 28 of the families showed an autosomal dominant transmission with reduced penetrance (81%). Nucleotide sequence analysis failed to uncover the missense mutation in the CHRNA4 gene previously reported, but did confirm two other base substitutions and supported the locus heterogeneity of ADFLE. (Oldani A, Zucconi M, Asselta R, et al. Autosomal dominant nocturnal frontal lobe epilepsy. A video-polysomnographic and genetic appraisal of 40 patients and delineation of the epileptic syndrome. Brain Feb 1998;121:205-223). (Respond: Alessandro Oldani MD, Sleep Disorders Centre, IRCCS H. San Raffaele, via Prinetti 29, 20127 Milano, Italy).

COMMENT. A report of electroclinical patterns in 33 patients with autosomal dominant frontal lobe epilepsy (ADFLE), including video-polysomnographic monitoring in 12, was published by these authors in 1996 (see Progress in Pediatric Neurology III, PNB Publ, 1997, pp87-88). The present report includes further patients and a genetic analysis of the syndrome. ADFLE is often misdiagnosed as nightmares, night terrors, or somnambulism. EEGs are frequently non-specific, and video-polysomnographic monitoring is important in the differentiation of ADFLE from parasomnias. A trial of antiepileptic drugs, carbamazepine or clonazepam, is warranted when the diagnosis is suspected, particularly in patients with diurnal symptoms.

SPECT studies in ADFLE. Frontal lobe foci were unilateral and in variable locations in two patients with ADFLE reported from the Department of Neurology, Austin and Repatriation Medical Centre, Heidelberg (Melbourne), Victoria 3084, Australia (Hayman M, et al. Neurology 1997;49:969-975). One case showed a left frontal onset corroborated by congruent focal hypometabolism on intercat PET and focal hyperperfusion on ictal SPECT. Another case studied with ictal SPECT showed a right parasagittal, midfrontal focus.