# SEIZURE DISORDERS

## ANTIEPILEPTIC DRUGS AND THYROID FUNCTION

Thyroid function in 78 girls and female adolescents (aged 8-18 years) during pubertal development was evaluated while taking carbamazepine (CBZ), oxcarbazepine (OXC), or valproate (VPA) monotherapy for epilepsy and after withdrawal of antiepileptic drugs, in a study at Oulu University Hospital, and Hospital for Sick Children and Adolescents, University of Helsinki, Finland. Examinations were repeated after a mean follow-up of 5.8 years. In the initial evaluation, the mean serum thyroid hormone concentrations were lower in the 19 girls taking CBZ (T4, 70.2; free T4, 11.5) or in 18 taking OXC (T4, 74.9; free T4, 11.3) than in the 54 control girls (T4, 96.6; free T4, 14.4), while TSH was normal in girls taking CBZ or OXC. Serum T4 and/or free T4 levels were below the lower reference range in 63% taking CBZ and 67% taking OXC. VPA-treated girls with epilepsy had normal T4 and free T4 levels but slightly increased TSH levels (3.3 compared to 2.5 in controls [$p<0.01$]). Serum hormone concentrations returned to normal after withdrawal of medication. (Vainionpaa LK, Mikkonen K, Rattya J, et al. Thyroid function in girls with epilepsy with carbamazepine, oxcarbazepine, or valproate monotherapy and after withdrawal of medication. **Epilepsia** March 2004;45:197-203). (Reprints: Dr LK Vainionpaa, Department of Pediatrics, FIN-90014, University of Oulu, Finland).

COMMENT. All the antiepileptic drugs studied had an effect on thyroid levels in girls during puberty, but the reductions in T4 and free T4 levels with CBZ and OXC, and the increase in TSH with VPA were reversed when the AEDs were withdrawn. Growth and pubertal development remained normal, and the hormonal changes had no effect on the clinical euthyroid state. Hepatic P450 enzyme induction and increased metabolism of thyroid hormones are proposed as one reason for the decreased thyroid levels during CBZ or OXC treatment. Variables in the methods of hormone analysis (commercial from diluted serum versus ultrafiltration method with undiluted serum) are also suggested as a possible explanation for some of the findings (Surks MI, DeFesi CR. **JAMA** 1996;275:1495-8).

**Lack of effect of AEDs on QT interval** in 178 children with epilepsy, ages 1 month to 18.9 years (Kwon S et al. **Pediatr Neurol** 2004;30:99-101). The mean corrected QT interval of 152 children on AEDs was 0.40+/-0.03 s, and for 26 AED-free control patients it was 0.40+/-0.03 s. There was no significant difference in QT intervals between drug groups (CBZ, OXC, VPA, TOP), monotherapy or polytherapy. AEDs are not a likely explanation for sudden unexpected death linked to prolonged QT in children with epilepsy.

## COGNITIVE OUTCOME OF ACTH-TREATED INFANTILE SPASMS

The long-term cognitive and seizure outcomes of 37 patients with cryptogenic infantile spasms (onset, age 3 to 9 months) treated with high-dose synthetic adrenocorticotropic hormone (ACTH) (1 mg IM every 48 hrs for 2 weeks, 8-10-week slow taper, followed by oral prednisone, 10 mg/d for 1 month, and slow taper for 5 months or until age 1 year) were evaluated at Schneider Children's Medical Center of Israel, Petah Tiqva,

Israel. Development was assessed before treatment and cognitive outcomes were determined after 6 to 21 years and analyzed in relation to treatment lag (after 1 month from onset) and pretreatment regression. Cognitive outcome was normal in all 22 (100%) infants treated within 1 month of onset of infantile spasms (early treatment group), and in 40% of 15 treated after 1 to 6.5 months (late-treatment group). Normal cognitive outcome occurred in all 25 (100%) with no or mild mental deterioration at onset, but in only 3 (25%) of 12 with severe pre-treatment deterioration. The prognosis for normal long-term cognitive outcome is poor if development has severely regressed for 1 month or more before treatment begins. (Kivity S, Lerman P, Ariel R et al. Long-term cognitive outcomes of a cohort of children with cryptogenic infantile spasms treated with high-dose adrenocorticotropic hormone. **Epilepsia** March 2004;45:255-262). (Reprints: Dr S Kivity, Pediatric Epilepsy Unit & EEG Laboratory, Schneider Children's Medical Center of Israel, Petah Tiqva, 49202, Israel).

COMMENT. In this series of cryptogenic cases, infantile spasms were permanently controlled in 92% of the early treated group and in 80% of the late treated group. Adverse effects were common with the high dose ACTH regimen: Cushingoid features developed in 100%, hypertension in >50%, and hypokalemia and infections were frequent occurrences. The authors justify the high-dose ACTH based on the results of a previous study showing poor results in patients treated with low-dose ACTH or corticosteroids (Lerman P, Kivity S. **J Pediatr** 1982;101:294-6).

The debate regarding low vs high dose ACTH for infantile spasms continues. My own preference like that of researchers in Japan has been for the low dose regimen, so that serious side effects are avoided (Millichap JG, Bickford RG. **JAMA** 1962;182:523-7; Ito M et al. **Pediatr Neurol** 1990;6:240-4). High doses are favored by colleagues in the UK and also by some in the US (Snead OC, et al. **Neurology** 1989;39:1027-31). The earlier diagnosis is made and ACTH treatment begun, the better the results. This is true with either regimen. Whether the incidence of relapse is less and cognitive outcome superior with large dose cf low dose treatment remains to be proven by a controlled trial.

## COGNITIVE OUTCOME OF HEMISPHERECTOMY

Long-term neuropsychological outcome was studied in 71 children who underwent hemispherectomy for severe and intractable seizures at the Johns Hopkins Hospital between 1968 and 1997. The cause of the seizures was cortical dysplasia in 27, Rasmussen syndrome in 37, and vascular malformation or stroke in 7. Mean age at surgery was 7.2 years. Seizures were completely controlled in 65% at average follow-up of 5.4 years, and 49% had discontinued medications. Mean IQ correlated with seizure etiology: 70s for Rasmussen and vascular patients, and 30s for cortical dysplasia patients. No significant change in cognitive measures occurred between surgery and follow-up. (Pulsifer MB, Brandt J, Salorio CF, et al. The cognitive outcome of hemispherectomy in 71 children. **Epilepsia** March 2004;45:243-254). (Reprints: Dr MB Pulsifer, Massachusetts General Hospital, Harvard Medical School, 5 Emerson Place, Suite 105, Boston, MA 02114).

COMMENT. Cognitive outcome in children with hemispherectomy for seizures is correlated with seizure etiology, patients with cortical dysplasia having lowest scores in intelligence and language while visual motor skills are relatively spared.