Baclofen Therapy May Be Associated with Chorea in Alzheimer's Disease

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The pathophysiological basis of chorea is not known. We encountered a patient with Alzheimer's disease (AD) who developed chorea during treatment with baclofen. The striatal cholinergic deficiency in AD may have made this subject especially likely to develop chorea with baclofen therapy.

Baclofen was being tried as a protective agent to slow the rate of progression of AD. The rationale for this treatment was provided by evidence that endogenous glutamate could act as a neurotoxin in AD [1]. Baclofen, a gamma aminobutyric acid (GABA) agonist, may decrease corticostriatal release of glutamate. If excess endogenous glutamate is deleterious in AD, and baclofen can reduce the rate of glutamate release, then baclofen therapy might have a protective effect and slow the rate of progression of AD.

A 76-year-old man with a 4-year history of progressive dementia consistent with probable AD gave assent to participate in an IRB-approved baclofen trial. Consent was provided by his wife and son. He scored 15 on the Blessed test of information, memory, and concentration and had no signs of motor dysfunction.

He was treated with baclofen, 5 mg three times a day, and the dose was increased over 2 weeks to 15 mg three times a day. Two days later the patient developed generalized chorea. The chorea stopped within 24 hours of baclofen withdrawal. The study was not continued in other subjects.

This patient may have been especially sensitive to effects of baclofen because of dysfunction of cholinergic interneurons in the striatum in AD [2]. Although association cortex and hippocampus are the major sites of cholinergic dysfunction, substantial cholinergic dysfunction in the striatum is found in AD. The combination of a GABA agonist and deficient cholinergic function may have led to decreased inhibition of output of neurons from the ventrolateral nucleus of the thalamus, which projects to the premotor cortex, and consequent chorea.

Shoulson and colleagues [3] reported that 3 of 30 subjects with Huntington's disease developed increased abnormal movements on baclofen therapy. Chorea has not otherwise been reported as a side effect of baclofen.

This observation is important for two reasons. First, combined treatments with anticholinergic agents and GABA agonists may be useful in creating animal models of chorea. Second, in future studies manipulating these systems in AD investigators should be wary of inducing chorea.

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Phosphorus Magnetic Resonance Spectroscopy of Brain in Mitochondrial Cytopathies

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In their recent report, Eleff and colleagues [1] claim that brain phosphocreatine concentrations measured by phosphorus magnetic resonance spectroscopy (MRS) are decreased in patients with mitochondrial cytopathies.

Our experience has been different. Using an ISIS technique for localized phosphorus MRS of brain [2] with resonance area measurement from fitting the free induction decay in the time domain, we reported last year that phosphocreatine/adenosine triphosphate (ATP) and inorganic phosphate/ATP concentration ratios were normal from central brain volumes in 6 patients with myoclonus epilepsy and ragged red fibers (MERRF) [3]. Central brain volumes of 3 more patients with MERRF and frontal volumes in 1 patient with MERRF and 1 patient with Kearns-Sayre syndrome have been studied with identical results. Five of these patients were studied with positron emission tomography and all had diffuse brain metabolic abnormalities [4].

Our observation of a normal energy state may reflect biological heterogeneity between patients or different regions of brain. However, the results obtained by Eleff with poor spectral localization based only on a surface coil may reflect differences in frontal, temporal, and ocular muscle bulk rather than in brain metabolism. As the phosphocreatine concentration of skeletal muscle is far greater (about 30 mM) than that of brain, even a small signal contribution from extracranial muscle could alter the observed phosphocreatine/ATP ratio significantly (e.g., a 4% signal contribution from skeletal muscle could increase the apparent phosphocreatine/ATP ratio from 1.5 to over 1.8). It is notable that the phosphocreatine/ATP ratio reported by Eleff and colleagues for normal controls (1.8) is higher than that found by us (1.4 ± 0.3, $n = 6$, $\pm$ SD) or others (1.4 [2], 1.2 ± 0.2 [5]). It is ultimately difficult to assess the likelihood of skeletal muscle contamination in the report of Eleff and associates. The applicability of the method cited for spatial localization is unclear. It relies on high-order static magnetic field gradients, which are not built into current imaging/spectroscopy magnets.

A second concern arises from the authors' claim that there were "multiple indications of abnormal metabolism." In fact, the only independent observation was the decreased phosphocreatine/ATP resonance intensity ratio. The brain [ADP] is calculated from this observation. The changes in

