Editors’ Note: Sethi suggests that neurology is mainly a clinical discipline. Dhand et al. explain that while many neurologic diagnoses are made clinically, some need additional laboratory, imaging, and electrophysiologic testing. The role of cortical cholinergic function on gait in patients with Parkinson disease is further elaborated by Mehanna. The role of acetylcholinesterase inhibitor drugs is, however, modest. Bohnen et al. suggest that drugs that selectively stimulate α4β2(*) nicotinic receptors may be more beneficial.

How Experienced Community Neurologists Make Diagnoses During Clinical Encounters

Nitin K. Sethi, New York: Dhand et al. studied the diagnostic practices of community neurologists. Experienced neurologists require little more than patient history supplemented by a general physical and neurologic examination to diagnose disease. They may confirm their diagnosis with the aid of various tests. Ideally, the model for the majority of neurologic diagnoses should be clinical (C) 4, laboratory (L) 1, and neuroimaging (N) 1. A shift to more testing (L4 N4) is due to many factors: the experience level of the neurologist, physician conflict of interest, fear of malpractice liability, and practice setting (academic center vs small community hospital). It would be interesting to replicate this study in different clinical settings in various countries.

Author Response: Amar Dhand, St. Louis; John Engstrom, Gurpreet Dhaliwal, San Francisco: We appreciate Dr. Sethi’s comments. Many diagnoses in neurology, like Parkinson disease, are dependent on the clinical domain. However, other conditions are only suggested by clinical findings but require neuroimaging (e.g., multiple sclerosis) or laboratory analysis (e.g., meningitis) to make the diagnosis. As we observed in these disorders, the imaging and laboratory components were equally as important as the information elicited by the history and examination. Therefore, we caution against advancing an overly classical view of neurologic diagnosis; one of the important findings from our study was the variance among disease types. We agree with Dr. Sethi that similar studies in other settings would be valuable.

Gait Speed in Parkinson Disease Correlates with Cholinergic Degeneration

Raja Mehanna, Houston: Bohnen et al. correlated slowing of gait with cortical cholinergic denervation, rather than nigral dopaminergic denervation, in patients with Parkinson disease (PD). This solidifies the current opinion that PD is the result of more than an isolated dopamine deficit. There was also no correlation with pedunculopontine nucleus (PPN)—thalamic denervation. The benefit of PPN-targeted deep brain stimulation on gait in PD is unclear. The authors suggested that enhancement of cortical cholinergic function might improve gait disorders in patients with PD. There are scare but promising data to support this suggestion.

A small open-label study of 9 patients with Alzheimer disease (AD) on galantamine for 6 months showed no improvement when patients only walked, yet it showed improvement when they walked and counted out loud. This confirms that the effect of denervation of the cholinergic system on gait might be through impairment of the attention and cognition (cortical), rather than the direct locomotion (PPN), network. However, these results could not be replicated in a smaller open-label study of 6 patients with AD treated with donepezil and 8 untreated patients with mild cognitive impairment serving as controls. Larger, randomized studies are needed.

Author Response: Nicolaas Bohnen, Martin Sarter, Martijn Muller, William Dauer, Roger Albin, Ann Arbor, MI: We agree with Dr. Mehanna that the clinical effects of acetylcholinesterase inhibitor drugs (AChEIs) are modest at best. Several factors may explain the limited effectiveness of AChEIs. First, our previous in vivo imaging studies have shown that in up to 60% of subjects with Alzheimer disease, AChEI-induced cerebral acetylcholinesterase inhibition may be too low to induce a relevant effect. Furthermore, when AChEIs elevate levels of acetylcholine in the brain, high synaptic and extrasynaptic acetylcholine levels may generate unwelcome effects, including...
inhibition of presynaptic cholinergic signaling by stimulation of presynaptic muscarinic type 2 receptors and nonphysiologic, tonic stimulation of postsynaptic nicotinic and muscarinic receptors.6 Despite these limitations, mobility benefits of AChEIs have been reported in PD.7

Preliminary data in animal studies suggest that drugs that selectively stimulate α4β2(*) nicotinic receptors not only have excellent entry into the brain but also may improve mobility functions in rats with dual dopaminergic and cholinergic lesions.8 Such selective agonists are superior to the nonselective nicotine mother drug because nicotine interferes with the phasic cholinergic activity that is essential for cognitive function.9 Further investigation of this class of drugs to treat mobility problems in PD is necessary.

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Raja Mehanna, Nicolaas Bohnen, Martin Sarter, et al.
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