

AGING OF THE NERVOUS SYSTEM

Aging of the Nervous System: Evolution, Genes, Aging, and Neurologic Disease

Evolution has not treated aging as an important biological event beyond the reproductive and parenting years. After the reproductive years, evolution has not provided a great deal of protection for enhanced survival. As a result, aging produces a permissive biological environment, allowing opportunistic disease processes to develop, including cerebrovascular disease, Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, the frontotemporal dementias, and progressive brain atrophy, among others. Neurologic disease associated with aging has become a major component of neurologic practice as the human life span increases. This issue of the ARCHIVES is dedicated to reviewing our knowledge about the "Aging of the Nervous System" and its consequences. Editorial reviews included in this theme issue are "Time and Memory" by Roger N. Rosenberg, MD, "The Evolutionary Substrate of Aging" by George M. Martin, MD, "The Genetics of Aging and Diseases: From Rare Mutations and Model Systems to Disease Prevention" by Victor D. Longo, PhD, and Caleb E. Finch, PhD, "The Endocrinology of Aging" by Steven W. J. Lamberts, MD, PhD, "Gene Expression Profile of the Aging Brain" by Richard Weindruch, PhD, and Tomas A. Prohla, PhD, "Regeneration in the Adult and Aging Brain" by Phillip J. Horner, PhD, and Fred Gage, PhD, and "Healthy Brain Aging" by Jeffrey Kaye, MD. As these articles show, increased emphasis in clinical and basic science research on the fundamental processes of brain aging will provide important clues about how and why specific neurologic diseases occur with age.

Predicting Parkinson Disease

The course of Parkinson disease (PD) is variable from patient to patient, and this variability has been the basis for studies to find accurate predictors of prognosis. Marras and colleagues (page 1724) have undertaken a careful systematic review to identify predictors of motor decline and disability in PD. Increased baseline severity of motor symptoms and early cognitive impairment were factors influencing progression of motor symptoms and disability. Increasing age and lack of rest tremor also seemed to predict more rapid accumulation of disability but not necessarily motor impairment. These were reliable correlations observed across the studies reviewed, and conflicting results were found concerning the prognostic importance of many other factors.

Mild Cognitive Impairment Equals Pre-Alzheimer Disease

Riemenschneider et al (page 1729) measured cerebrospinal fluid (CSF) levels of tau and β -amyloid 42 ($A\beta_{42}$) in 28 patients with mild cognitive impairment (MCI) for 18 months to correlate these levels with progression to Alzheimer disease (AD). Twelve of 28 patients with MCI progressed to dementia. Six patients had progressive MCI and 10 had stable MCI. Tau levels in CSF were significantly elevated in patients who progressed to probable AD and in patients with progressive MCI compared with patients with stable MCI. $A\beta_{42}$ levels in CSF were significantly lower in patients who progressed to probable AD and in those with progressive MCI than in patients with stable MCI. Thus, these findings strongly support the view that MCI is a prelude to AD in some patients who have MCI with altered CSF levels of tau and $A\beta_{42}$. This is an important clinical and CSF diagnostic study showing the spectrum of altered cognition from MCI to AD. *Editorial comment is provided by Roger N. Rosenberg, MD.*

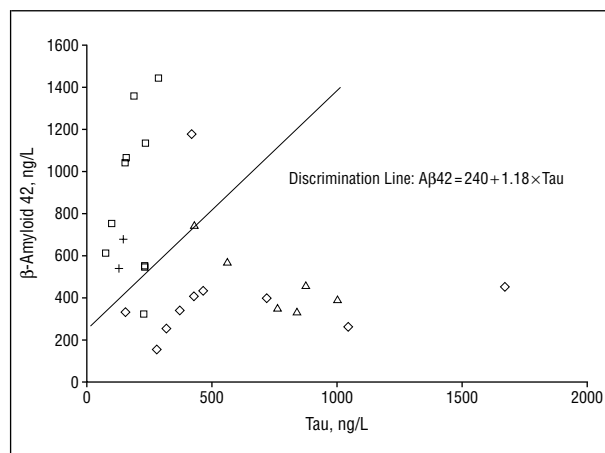


Figure 3. Scatter plot of cerebrospinal fluid tau and β -amyloid 42 ($A\beta_{42}$) concentrations in subjects with mild cognitive impairment (MCI) at baseline by diagnosis at 18-month follow-up. The line within the figure indicates the best discrimination line. Squares indicate stable MCI; plus signs, frontotemporal dementia; triangles, progressive MCI; and diamonds, Alzheimer disease.

Marking Alzheimer Disease

Kukull and colleagues (page 1737) provide a rigorous study that definitively shows the age-specific incidence estimates for dementia and Alzheimer disease (AD) and the association of sex, education, and apolipoprotein E genotype with onset. They report that the incidence rates for dementia and AD increase across the 5-year age groups—AD rates rise from 2.8 per 1000 per

son-years (age 65-69 years) to 56.1 per 1000 person-years (age \geq 90 years). Sex was not associated with AD onset. Education (>15 vs <12 years) was associated with decreased risk of AD. This comprehensive and thorough analysis of incidence rates for dementia and AD will provide the researcher and physician a stronger foundation from which to address age-associated risks of dementia and AD.

Testosterone and Parkinson Disease

It has been noted by several grateful male patients with Parkinson disease (PD) that testosterone replacement therapy has beneficial effects on cognitive function and other nonmotor symptoms. Okun et al (page 1750) studied 10 patients with PD who were taking daily testosterone replacement therapy for 1 month and 6 patients for 3 months. Serum testosterone levels increased and testosterone deficiency symptoms improved, including libido, energy, enjoyment, and work performance. The basis for these improvements with testosterone replacement therapy need to be studied further but nevertheless represent a new dynamic in the overall evaluation and care of the patient with PD.

Mutations Causing Alzheimer Disease

Leó and colleagues (page 1759) have studied the relative contribution of mutations in the presenilin and amyloid precursor protein genes to autosomal dominant and other early-onset forms of Alzheimer disease (AD) in families and patients in Spain. Ninety-four patients with AD from 82 independent families were studied. They found that more than half of the families with autosomal dominant early-onset AD had presenilin gene mutations. This study brings new data on this subject and emphasizes the importance of population screening for presenilin mutations in families with early-onset AD.

Surviving Alzheimer Disease

Brookmeyer et al (page 1764) show that the effect of a diagnosis of Alzheimer disease (AD) on life span depends on the age at diagnosis. The median life span is 7 to 10 years for patients receiving this diagnosis in their 60s and early 70s but only 3 years or less for patients receiving this diagnosis in their 90s. On the surface, these numbers seem intuitively correct, but it is important to rigorously define this issue to provide resources for the increasing numbers of patients with AD expected in the next 25 years.

Amyloid Neuropathy: Early and Late Forms

Koike et al (page 1771) have characterized the clinical features of patients in Japan with amyloid neuropathy and the transthyretin Met30 mutation. Early- and late-onset forms were discovered, with spe-

cific and different clinical findings. It is of interest to see that divergence of clinical features with a common mutation pointing out genetic polymorphisms and the environment play crucial roles in disease expression.

Freezing Gait

Factor and colleagues (page 1778) have analyzed the natural history, clinical, and brain imaging characteristics and responses to dopaminergic medications in patients with primary progressive freezing gait disorder (PPFG). They believe that PPFG is a clinically distinct neurologic disorder associated with other parkinsonian features, particularly bradykinesia, and is unresponsive to dopaminergic medications. It is their view that PPFG is a Parkinson-plus disorder.

Parkinson-Plantation-Pesticide Syndrome

Petrovitch et al (page 1787) studied the occurrence of Parkinson disease (PD) among plantation workers in Hawaii who were exposed to pesticides. Participants were 7986 Japanese American men born between 1900 and 1919. One hundred sixteen men developed PD. The age-adjusted incidence of PD increased over time in those who worked on a plantation, and the age-adjusted incidence of PD was higher in men exposed to pesticides, although this latter association was not statistically significant. Further detailed pesticide associations are needed to establish causation but this study has increased public awareness of the issue and potential work-related risk of exposure to pesticides.

Polymorphisms in the Amyloid Gene for Alzheimer Disease

Athan et al (page 1793) have investigated the possibility that polymorphisms in regulatory sequences of the amyloid precursor protein gene are susceptible to early-onset Alzheimer disease. No significant polymorphisms were found in this region. This negative study has yielded important information on this issue.

Dementia in Machado-Joseph Disease

Ishikawa et al (page 1804) have studied cognitive impairment and dementia in dominantly inherited cerebellar degeneration of the autosomal dominant Machado-Joseph disease (MJD) type in Japan. It occurred in a cohort of patients with a CAG repeat length in the *MJD1* gene that was longer than the mean repeat length found in the patients with MJD. Polyglutamine inclusions in cerebral cortical neuronal nuclei were found in 2 patients with MJD with primary cerebellar degeneration. Cognitive loss may be related to cerebrocortical neuronal dysfunction due to neuronal nuclear inclusions rather than neuronal loss.