

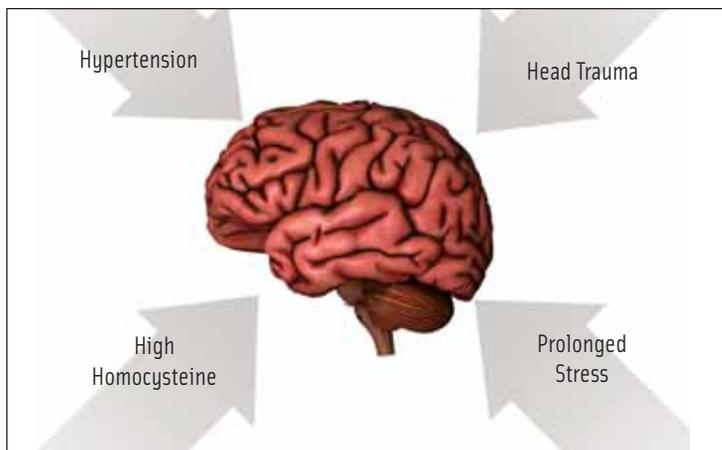
# How Accurate is Alzheimer's Diagnosis Among Patients over 80?

A mixture of multiple pathologies may contribute to dementia in most elderly beyond the age of 80.

By Majid Fotuhi, MD, PhD

**T**he age-old question of why some elderly in their 80s and 90s remain cognitively sharp while other elderly develop dementia remains a puzzle. A new study offers a fresh challenge to the notion that Alzheimer pathology is the key culprit. Increasing forgetfulness and confusion among those older than 80 was documented as early as 7th century BC by Greek philosopher Pythagoras, who considered it a “return to imbecility of infancy”.<sup>1</sup> During each subsequent era, various hypotheses were heralded as the main etiology for late-life cognitive decline, ranging from “normal aging” to demonic possession, to syphilis, to strokes, to hardening of the blood vessels, and—since the late 20th century—to Alzheimer disease. “Senile dementia,” the term commonly used in the last two centuries, has become almost synonymous with Alzheimer disease.<sup>1</sup>

The discovery that  $\beta$ -amyloid aggregation in the brain may be at the heart of a series of steps in a biochemical cascade that leads to dementia raised



The brain is resilient and can resist the effects of “hits” that lead to cortical atrophy. The hits may include a range of genetic and biological factors such as Apolipoprotein genotype, hypertension, prolonged stress, and head trauma. When multiple factors harm the brain at the same time and when protective factors (cognitive reserve) are limited, patients develop cognitive impairment. The more “hits” the brain gets, the sooner it decompensates.

*Fotuhi M. The Memory Cure: How to Protect your Brain against Memory Loss and Alzheimer's Disease. New York: McGraw Hill, 2003, with permission.*

the hope for therapeutic interventions that one day could ease, or even end, late-life cognitive impairment.<sup>2</sup> However, in the past two to three

years, an Alzheimer-centric view of the brain with aging has been questioned. For example, pathological findings in large prospective studies have revealed similar degrees of plaques and tangles in the brains of elderly with dementia as in those without dementia.<sup>3</sup> In fact, a substantial number of elderly beyond the age of 80 may have severe neuropathologic hallmarks of Alzheimer disease without any clinical evidence of dementia.<sup>4</sup> Some vaccines have been successful in clearing amyloid plaques in the brain, but they have failed to slow or reverse any symptoms of dementia.<sup>5</sup> Thus, the simple theory that late-life dementia is merely an Alzheimer issue is vanishing.

To complicate matters further, it appears that those prescribed antihypertensive medications may have less Alzheimer neuropathology in their brains than those who do not experience hypertension.<sup>6</sup> Moreover, ischemia and hypoxia can contribute to atrophy in the hippocampus, independent of plaques and tangles.<sup>7</sup> Such findings have begun to blur the distinctions between vascular dementia, Alzheimer dementia, Normal Pressure Hydrocephalus, Lewy Body dementia, and the other potential causes for late-life dementia.<sup>8</sup> It appears that most elderly beyond the age of 80 have a mixture of multiple pathologies that contributes to their dementia.<sup>3</sup>

### **The Evidence**

A new study by Savva, Wharton, et al. from the Medical Research Council in England offers a fresh blow to the concept that Alzheimer pathology is the primary cause of cognitive impairment in elderly beyond the age of 80.<sup>9</sup> The researchers performed detailed clinical-pathological evaluation of 456 elderly who had donated their brains for a longitudinal Cognitive Function in Ageing Study. Many of their findings are exactly opposite of what would have been expected based on the current views of late-life dementia. They show that the significance and relevance of plaques and tangles are age dependent. The association between Alzheimer pathology and dementia progressively weakens as people approach their late 90s. In elderly

with dementia, the amount of plaques and tangles actually appears to decrease or remain constant in the hippocampus and neocortical areas. In elderly without dementia, the levels of Alzheimer pathology increase with each decade of life. In agreement with a number of other recent studies,<sup>4</sup> this new study reports that the degree of atrophy in cortex and hippocampus remains the variable that best correlates with dementia—at any age.

As noted by Alois Alzheimer, the pathophysiology of dementia in a 55-year-old patient is quite different than that in an 85-year-old patient. He wrote: “Plaques are not the cause of senile dementia, but only an accompanying feature of senile involution of the central nervous system.”<sup>10</sup> In those with early-onset dementia, plaques and tangles are the main culprits. In those with late-onset dementia, especially those beyond the age of 80 or 90, plaques and tangles are most likely co-players in causing brain atrophy, which is the real culprit.

The focus for finding etiologies for late-life dementia is now turning from what causes the accumulation of plaques and tangles to what causes cortical and hippocampal atrophy. One possibility is that a dynamic interaction of multiple pathological processes (including plaques, tangles, Lewy bodies, inflammation, exposure to various medications, and vascular injury from minor to large strokes) reduces the size of both cortex and hippocampus.

A recent clinicopathological study involving the analysis of 443 autopsies in individuals with detailed known clinical course shows that only 18.6 percent of elderly had Alzheimer pathology as the sole or dominant lesion to account for their dementia.<sup>11</sup> Microvascular infarcts were the sole or dominant lesion in 14.2 percent of the participants with dementia while 87.9 percent had mixed pathologies.<sup>11</sup> Thus, brain resilience may tolerate a certain degree of injuries caused by genetic and environmental hits, until a certain threshold is reached. At that point, cognitive abilities fall apart and the patient develops dementia (Fig 1).

Another possibility is that the real culprit (factor X) may have not yet been discovered. In the early 1980s, *Helicobacter pylori* bacterium was identified as the real cause of peptic ulcer disease and thus completely changed our understanding of, and therapeutic approaches toward, this common condition. With regard to late-life dementia, we must keep an open mind and consider other factors (e.g., activation of new late-life genes, fail-

ure of protective repair mechanisms, accumulation of toxic metabolites, mitochondrial disease, and/or impairment of control over protein aggregation) that can bring about brain atrophy with aging. Pursuing therapeutic interventions that affect amyloid may be useful for a small portion of the population that has early-onset dementia but most likely would have minimal effect for tens of millions of patients with late-life dementia.

### More Questions: Therapeutic Targets in AD

There continues to be speculation about the ideal therapeutic targets in Alzheimer's disease, with current investigation into vaccines and treatments largely focused on amyloid beta and some researchers turning their sights on tau. Rember, from TauRx, is in clinical development and reportedly shows promise as a Tau aggregation inhibitor. The company says the agent dissolves tau aggregates and prevents the aggregation process. Just last month, researchers from another tau-focused study reported<sup>1</sup> that inhibiting Hsp70 ATPase activity led to rapid degradation of tau in a chemical model and reduced tau levels in brain tissue from murine models of AD.

In the field of amyloid-beta development, Israeli researchers working on a vaccine for AD "demonstrated that it is possible to test and measure specific immune responses in mice carrying human genes and to anticipate the immune response in Alzheimer's patients." Late last month, researchers at Ben-Gurion University of the Negev demonstrated that the specificity and magnitude of this body response to A-beta depends on certain key genes of the immune system. Their research combined humans and humanized mouse models. "Conceivably, those people that have this gene could receive the same vaccine which will teach a person's immune system to better fight the disease," says researcher Alon Monsonego in a statement. "As in other mouse models of the disease, we show that with aging Amyloid- $\beta$  aggregates accumulate in brain areas of cognitive functions and stimulate an inflammatory reaction in the brain." However, stimulating an immune response to

Amyloid- $\beta$  in these humanized mice not only resulted in a highly efficient clearance of Amyloid- $\beta$  from the brain, but also in a marked reduction in inflammatory reaction.

Some research suggests that supplementation of the hormone melatonin may be effective against amyloid. This connection with melatonin is strengthened by recent research that shows the wakefulness inducing hormone orexin influences beta amyloid. A study by Wang et al., looked at the effect of melatonin (Mt) and melatonin derivative, i.e., melatoninvalpromide (Mtv), on cell viability,  $\beta$ -amyloid ( $A\beta$ ) production, cell morphology, and expression and phosphorylation of neurofilament proteins in wild-type murine neuroblastoma N2a (N2a/wt) and N2a stably transfected with amyloid precursor protein (N2a/APP) cell lines.<sup>2</sup> Using MTT assay, Sandwich ELISA, immunocytochemistry and Western blots techniques, the results showed that both Mt and Mtv could increase cell viability, but Mtv did so more effectively.

The N2a/APP demonstrated shorter and less amounts of cell processes than N2a/wt, and Mtv slightly improved the morphological changes in N2A/APP while Mt did not. Both Mt and Mtv suppressed the  $A\beta$  level in cell lysates, but the authors found the effect of Mtv was stronger than Mt. "The immunoreaction to the non-phosphorylated neurofilament proteins probed by SMI32 and SMI33 were remarkably weaker in N2a/APP than N2a/wt," the researchers write, "while the immunoreaction to the phosphorylated neurofilament proteins at SMI34 epitopes was slightly stronger in N2a/APP than N2a/wt, suggesting higher phosphorylation level of neurofil-

## Rethinking Diagnoses

Recent studies challenge the accuracy of a diagnosis of Alzheimer disease for those in their 80s and 90s. If mixed pathologies (not plaques and tangles) account for their dementia, it would be more honest and accurate to label them as having dementia (or alternatively mild, intermediate, or severe cognitive impairment) until a specific and dominant pathological feature is identified. Clearly, the old-

est old do not simply have Alzheimer disease. The high likelihood of heterogeneity of causes for late-life dementia must also serve as a sobering warning for researchers who are trying to identify a single "early" biochemical marker for elderly at risk for developing dementia in the future.

In summary, "the emperor has no clothes." The burgeoning literature, coalescing in the Savva paper, leads one to conclude that Alzheimer disease is, as Dr. Alzheimer dubbed it, a "presenile dementia" and that there is no definitive evidence that Alzheimer's pathology is truly causal in dementia of the "elderly." Thus, we need to be cautious in making a diagnosis of Alzheimer disease in our 80+ patients. Dementia, or ideally Cognitive Impairment, may be the preferred diagnostic terminology. ■

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ament proteins in N2a/APP."

Treatment of the cells with Mt and Mtv increased the immunoreaction at SMI32 and SMI33 epitopes, while only Mtv-and not Mt-decreased the staining at SMI34 epitope, which the authors write suggests both Mt and Mtv promote dephosphorylation of neurofilament at SMI32 and SMI33 epitopes, while Mtv stimulates dephosphorylation of neurofilament at SMI34 epitope. "These results suggest that Mtv may be a better candidate in arresting the intracellular accumulation of A $\beta$  and protecting the cells from A $\beta$ -related toxicity."

A second study using in vivo microdialysis in mice found that ISF A $\beta$  levels correlated with wakefulness.<sup>3</sup> Brain interstitial fluid A $\beta$  levels also significantly increased during acute sleep deprivation and during orexin infusion, yet decreased with infusion of a dual orexin receptor antagonist, the authors found. "Chronic sleep restriction significantly increased, and a dual orexin receptor antagonist decreased, A $\beta$  plaque formation in amyloid precursor protein transgenic mice," they write. "Thus, the sleep-wake cycle and orexin may play a role in the pathogenesis of AD."

—Zac Haughn  
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