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GUEST EDITORIAL

Age, Alzheimer's disease, and the big picture

The recently published revised National Institute on Aging/Alzheimer's Association clinical diagnostic criteria for Alzheimer's disease (AD) (Albert *et al.*, 2011; Jack *et al.*, 2011; McKhann *et al.*, 2011; Sperling *et al.*, 2011) have been hailed for incorporating a number of timely and important advances. They reflect new understanding that has been gained since the previous criteria were published in 1984 (McKhann *et al.*, 1984). They include recognition of the state of mild cognitive impairment that is present before the threshold is crossed into dementia; they recognize the potential role of biomarkers in enhancing the specificity of diagnosis; they also address emerging work in the preclinical stage of AD that could help in understanding the sequence and stages of the core pathology before symptoms emerge. Among the previously listed diagnostic features that have disappeared was the requirement that onset of dementia occur before the age of 90 years. Meanwhile, the Neurocognitive Disorders Work Group for DSM-5 (the 5th edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*; American Psychiatric Association, 2010) is also doing away with the previous distinction between early-onset and late-onset dementia in AD, where an arbitrary division had been placed at age 65 (American Psychiatric Association, 2000). These changes are driven by the lack of biological data to support the age-based dichotomy, while recognizing the unique genetic characteristics of the relatively rare, autosomal dominantly inherited forms of AD which typically occur early. However, the disappearance of the age-based diagnostic dichotomy by no means implies that age is irrelevant to AD.

Epidemiology examines the distribution of disease at the population level, and the epidemiologist's role is therefore to step back and look at the big picture. Population studies find that the incidence of AD increases exponentially with age and does not stop at age 90, although few studies have included enough individuals over that age to determine whether the incidence rate levels off or continues to rise (Jorm and Jolley, 1998; Gao *et al.*, 1998). As life expectancy rises the world over (Kinsella and Wan, 2009), the largest and fastest-growing proportion of people with clinical AD are in the oldest age group however that group is defined (Ferri *et al.*, 2005; Alzheimer's Disease International, 2010)

Epidemiologists also seek to identify the factors which drive the observed distribution of disease, i.e. those that appear to increase or reduce the probability ("risk") of developing disease. Since aging is associated with increased incidence of AD, it behooves us to explore age-related differences in risk factors for AD across the spectrum from early-onset to "late-late" onset AD. As population-based cohorts are observed over many years, a curious pattern emerging from longitudinal studies might support the following model.

Let us conceptualize clinical AD as falling into not two but three groups based on age at onset: the young group, with symptom onset roughly between ages 40 and 60, an intermediate group with onset in what might be termed early old age (say, 60 to 85 years), and a late old age group with clinical onset after age 85.

In the young-onset group, positive family history and identified autosomal dominant genes are the best-known primary risk factors (Kamboh, 2004). Occasional, apparently sporadic cases of AD in younger persons may be found on further investigation to represent previously unrecognized genetic mutations (Bartram *et al.*, 2010). Exposures such as head trauma may hasten the onset of symptoms (van den Heuvel *et al.*, 2007) but, for the most part, early-onset AD might be considered AD in pure culture; other comorbid diseases are rarely present to the extent that they confound the clinical picture.

In the intermediate-onset group, a number of risk factors have been identified: the *APOE*4* genotype (Corder *et al.*, 1993), cardiovascular and cerebrovascular disease, high blood pressure, diabetes mellitus, higher cholesterol and body mass index, typically observed during midlife (Craft, 2009; Hughes and Ganguli, 2009). Vascular comorbidity is the norm rather than the exception in this intermediate group (Schneider *et al.*, 2007), a fact which has bedeviled development of diagnostic criteria for cognitive impairment and dementia of vascular origin (O'Brien, 2006). It seems likely that the presence of vascular disease promotes the clinical expression of dementia of AD type (Dodge *et al.*, 2011).

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In the oldest-onset group, however, it appears that no risk factor other than increasing age is associated with developing AD (Kuller and Lopez, 2009; 2011). Vascular disease is frequently present along with AD but some degree of vascular disease is almost ubiquitous in the ninth and tenth decades of life (Price *et al.*, 1997; de Leeuw *et al.*, 2001; Vermeer *et al.*, 2002). Further, diffuse amyloid plaques are present in the brains of many older adults who do not have other pathologic or clinical evidence of AD (Aizenstein *et al.*, 2008; Price *et al.*, 2009). The *APOE*4* genotype, already neither a necessary nor sufficient cause at earlier ages, appears to have exhausted its predictive power impact by age 80 or so. The contribution of other postulated genetic factors to population-attributable risk, even in the larger late-onset AD population, seems small (Naj *et al.*, 2011).

We now possess the means to plot AD progression, including preclinical disease, along several axes (e.g. clinical stages, CSF biomarker levels, structural and functional brain changes as evident on neuroimaging) (Albert *et al.*, 2011; Jack *et al.*, 2011; McKhann *et al.*, 2011; Sperling *et al.*, 2011). We propose that aging itself constitutes another dimension for describing or predicting expected features of the disease, in effect distinguishing subtypes of the disease, by their pathogenesis, pathology, and pathophysiology. Thus, age, or a variety of neurologic changes for which age serves as surrogate and sole identified cause, is associated with variant forms (subspecies or perhaps distinct "species") of what investigators often treat as a unitary disease.

So, for example, the role of deterministic genes is greatest at youngest ages and decreases with age. Brain reserve and cognitive reserve (Katzman, 1993; Stern, 2002), by buffering brain function against progressive pathologic change, may play a role in determining age at "onset," i.e. the age at which disease becomes clinically manifest. With increasing age, comorbid disease and aging-related changes such as decreased synaptic density (Masliah *et al.*, 2006) and reduced synaptic plasticity (Lister and Barnes, 2009) play greater roles in promoting both Alzheimer-type and non-specific pathology. Late-onset dementia, then, would be dementia whose onset has been delayed by greater reserve, the absence of strong genetic determinants, and favorable risk factor profiles. Clinical dementia emerges when protective factors have been depleted, and the burden of disease and age-related brain pathology has become heavy, with a more diverse and less AD-specific neuropathology than seen in younger persons (Stricker *et al.*, 2011). In fact, growing evidence documents an age-associated weakening of the association between Alzheimer's pathology and clinical dementia: while typical Alzheimer's pathology becomes more prevalent with age in persons without dementia, members of the "old-old" set with dementia have burdens of typical pathology similar to that of their normal counterparts (Savva *et al.*, 2009).

The current situation has recently been summed up as supporting "three major hypotheses related to dementia: amyloid deposition and secondary synaptic loss, as a unique disease; vascular injury; and 'aging'" (Kuller and Lopez, 2011). But how do we prevent "aging"? And what might be the implications for potential prevention and treatment strategies for AD?

In the young-onset group, those at genetic risk can be identified for prevention or early intervention. Unless the appropriate gene therapy can be devised, the common therapeutic goal would be to strike early at the key disease-promoting pathway – for example, interfering with the production and aggregation of insoluble beta amyloid protein (Rafii and Aisen, 2009; Golde *et al.*, 2009) and possibly tau phosphorylation (Schneider and Mandelkow, 2008) in the brain.

In the intermediate-onset group, the goals might include similar efforts at prevention as in young onset patients. But, especially when preclinical disease is suspected based on the detection of amyloid biomarkers, therapies may also be designed to undo already existing disease, for example, by promoting clearance and excretion of already deposited amyloid (Rafii and Aisen; 2009; Mawuenyega *et al.*, 2010) and tau (Schneider and Mandelkow, 2008) proteins. In this group there might also be benefits to controlling inflammation and vascular risk (Craft, 2009), so that even if insoluble amyloid and hyperphosphorylated tau proteins have begun to accumulate, clinical expression of the dementia can be delayed or prevented.

The oldest-onset group presents a different and more formidable challenge, because their only risk factor is age, or, stated otherwise, they have yet to demonstrate a "preventable determinant" (Kuller and Lopez, 2009). In this group, the much-sought agents which interrupt the amyloid pathway may slow Alzheimer-type pathogenesis without having a proportionate impact on incident dementia. Given the complex etiology of dementia in the very old, extrapolating from "cleaner" pathophysiologic models derived from the study of younger patients may not yield insights likely to produce effective therapies for the very old.

The final, somewhat ironic, twist in the plot is that the youngest group is very small while the oldest group is the largest and fastest growing (Kinsella and Wan, 2009). Thus, in terms of the potential

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market for pharmaceutical treatment of AD, the largest group of customers may be the one in which treatment targeting amyloid pathways may prove the least likely to be effective. Meanwhile, the early-onset population, in which disease-specific, even pathway-specific, interventions seem the most promising, is so small that true anti-AD agents may be virtual "orphan drugs." Like most syndromes of the elderly, dementia of AD type in the oldest-old may be a disorder of multifactorial causation, with causes including multiple and perhaps ineluctable aging processes. In that case, prospects for meaningfully effective intervention may be least likely in the very population which largely drives the dire predictions regarding the looming societal costs of health care for AD (Alzheimer's Disease International, 2010).

The aesthetically less than satisfying reality may be that prevention and treatment of AD in the very old will involve searching out therapeutic footholds in a variety of contributory disorders. The objective may be to delay onset and attenuate clinical severity rather than to attack a central, even singular, cause. Perhaps the giant against whom we struggle is less like Goliath, to be felled by a single strategically placed pebble from a slingshot, and more like Gulliver, to be wounded and contained by a myriad Lilliputian arrows and shackles.

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