Late-Life Depression Research: Lessons Learned From the Metabolic Syndrome

Recent U.S. Census Bureau data tell us there are approximately 40 million adults over the age of 65. This is already a formidable statistic, yet it will rise rapidly over the next two decades as the cohort of baby boomers continues to age. Among individuals currently over age 65, 14.2 million live with some type of disability in self-care, cognition, ambulation, hearing, vision, or other function (1). Consequently there is a pressing need to understand the various processes that may interfere with independence and quality of life in older adults. Without question, depression is a source of disability in late life; despite extensive research, a complete understanding of its pathogenesis and treatment response has remained elusive.

In this issue, Sheline et al. (2) examine the time course of treatment response in late-life depression and integrate their observations with measures of structural imaging volumes, neuropsychological function, and vascular disease risk. The authors duly note that "the vascular depression hypothesis posits that cerebrovascular disease contributes to the development and severity of depression in older adults by causing ischemic white matter lesions" (3, 4), which may disrupt neural connections relevant to mood regulation and cognitive function. Along these lines, a previous report by Sheline et al. (5) found that measures of cognitive function and white matter hyperintensities predicted depression severity ratings over time in persons receiving treatment for late-life depression. However, the earlier study did not examine gray matter regions of interest.

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The current Sheline et al. study (2) finds that smaller hippocampal volumes predicted a slower rate of treatment response within a 12-week sertraline trial. Using a model examining multiple factors that may influence treatment outcome, the authors included neuropsychological scores and determined that the best model to predict the rate of change in measures of depression severity involved hippocampal volume and cognitive processing speed. To determine whether the hippocampal volume predictor was independent of vascular risk, a post hoc analysis included a vascular risk factor score in the model, and smaller hippocampal volumes remained a significant predictor of the duration to treatment response.

The role of the hippocampus in mood disorders has been examined extensively (6), such that hippocampal gray matter loss may be considered a defining feature of depression (7). However, there have been inconsistencies in this literature, and it has been observed that the majority of studies reporting evidence of hippocampal atrophy have used samples comprising elderly, middle-aged, or chronically ill individuals (8); hence, the finding may reflect the deleterious effects of excessive glucocorticoid and excitotoxic amino acid activity as a consequence of long-standing recurrent depressive episodes. Certainly, recurrent depressive

illness may have pathogenic consequences; however, in the elderly population, the additional potential impact of neural aging, vascular disease, and Alzheimer's pathology constitute a complex multifactorial milieu of risk factors that may each result in impaired mood regulation.

This interaction of multiple risk factors calls for a careful look at pathological processes that may have synergistic effects. The research unraveling the key factors leading to coronary artery disease may yield some clues as to how to approach the factors that may lead to late-life depression. In 1988, Gerald Reaven detailed a condition initially called "syndrome X," which turned out to have a far-reaching effect across medicine, including the field of psychiatry (9). The term was first coined to describe cardiac patients who did not have large coronary vessel stenosis but nonetheless had ischemic heart disease, reflecting an emerging awareness of microvascular changes (10). Subsequent studies determined that a cluster of factors associated with insulin resistance comprise a syndrome, which plays an important role in the clinical course of diabetes, hypertension, and coronary heart disease (11). Resulting from this seminal work is the now commonly recognized "metabolic syndrome" (12), which has had tremendous implications for the adverse medical outcomes of chronic psychotropic interventions, and its components also include risk factors known to influence both vascular depression and dementia.

Of relevance to the future direction of late-life depression research is a recent reflection by Reaven (13) in which he questioned the clinical utility of ongoing research associating risk factors in the absence of studies of pathogenesis. He noted that "despite the enormous number of publications devoted to the MetS [metabolic syndrome] and the enthusiastic support of the prestigious scientific organizations…belief that a diagnosis of MetS is useful is not shared by all." He concludes that "it can be argued that none of this information has provided new pathophysiological insight, nor does it support the clinical utility of the MetS as a diagnostic category" (13). Our understanding of late-life depression similarly faces the challenge of reaching beyond examining a confluence of risk factors and moving toward an understanding of pathogenesis. The study by Sheline et al. represents one step in doing just that, but additional work exploring specific pathogenic processes affecting the hippocampus in late life may be the essential next step.

Certainly, gray matter loss may be due to interruptions in white matter connections, and future advances in diffusion tensor tractography are needed to confirm this premise. However, low hippocampal volumes may also signal the overlap between brain changes associated with Alzheimer's dementia and late-life depression. While the Sheline et al. study specifically excluded patients who demonstrated evidence of functional decline that would be consistent with dementia, it is increasingly clear from large-scale studies such as the Alzheimer's Disease Neuroimaging Initiative (14) that a variety of biomarkers may show abnormalities long before changes in cognition or daily function may be detected. Research in this area has demonstrated that gray matter volume loss may be observed in individuals prior to progression to the clinical states of mild cognitive impairment, and measures of Alzheimer's pathology via CSF amyloid and tau levels and amyloid imaging may similarly be detected years before cognitive or functional decline (15, 16). Moreover, depressive symptoms in the context of mild cognitive impairment appear to predict progression to Alzheimer's dementia (17), and a recent large epidemiological study suggests that depression appearing for

the first time in late life may signal the Alzheimer's prodrome (18). Rapid advances in research demonstrating that vascular disease accelerates amyloid pathology provide yet another reason to broaden our thinking about late-life depression (19). It is essential that future research incorporate biomarkers to help "drill down" to the various mechanisms that may be afoot in the older adult displaying mood changes. If we miss the opportunity to do so, we may (as Reaven suggested regarding the metabolic syndrome) end up with a menu of risk factors that is no more useful in aggregate than its individual parts.

In sum, the field of late-life neuropsychiatry is now at a place where it is necessary to extend beyond research showing that one factor predicts another (i.e., that late-life depression predicts cognitive decline or that cognitive changes predict worse depression) and move toward the understanding that both the manifestation of mood symptoms and cognitive changes may be derived from the same underlying pathologic processes. It is the understanding of these processes that will lead to disease-modifying treatments as opposed to symptomatic care.

References

1. US Census Bureau: Statistical Abstract of the United States: 2012, 131st ed. Washington, DC, US Government Printing Office, 2011
2. Sheline YI, Disabato BM, Hranilovich J, Morris C, D'Angelo G, Pieper C, Toffanin T, Taylor WD, MacFall JR, Wilkins C, Barch DM, Welsh-Bohmer KA, Steffens DC, Krishnan RR, Doraiswamy PM: Treatment course with antidepressant therapy in late-life depression. Am J Psychiatry 2012; 169:1185–1193
3. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M: "Vascular depression" hypothesis. Arch Gen Psychiatry 1997; 54:915–922
4. Krishnan KR, Hays JC, Blazer DG: MRI-defined vascular depression. Am J Psychiatry 1997; 154:497–501
5. Sheline YI, Pieper CF, Barch DM, Welsh-Bohmer K, McKinstry RC, MacFall JR, D'Angelo G, Garcia KS, Gersing K, Wilkins C, Taylor W, Steffens DC, Krishnan RR, Doraiswamy PM: Support for the vascular depression hypothesis in late-life depression: results of a 2-site, prospective, antidepressant treatment trial. Arch Gen Psychiatry 2010; 67:277–285
6. Drevets WC, Price JL, Furey ML: Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct Funct 2008; 213:93–118
7. Campbell S, Marriott M, Nahmias C, MacQueen GM: Lower hippocampal volume in patients suffering from depression: a meta-analysis. Am J Psychiatry 2004; 161:598–607
8. Savitz J, Drevets WC: Bipolar and major depressive disorder: neuroimaging the developmental-degenerative divide. Neurosci Biobehav Rev 2009; 33:699–771
9. Reaven GM: Banting lecture 1988: role of insulin resistance in human disease. Diabetes 1988; 37: 1595–1607
10. Kemp HG Jr: Left ventricular function in patients with the anginal syndrome and normal coronary arteriograms. Am J Cardiol 1973; 32:375–376
11. Reaven GM: Role of insulin resistance in human disease (syndrome X): an expanded definition. Annu Rev Med 1993; 44:121–131
12. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity: Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009; 120:1640–1645
13. Reaven GM: The metabolic syndrome: time to get off the merry-go-round? J Intern Med 2011; 269: 127–136
14. Weiner MW, Veitch DP, Aisen PS, Beckett LA, Cairns NJ, Green RC, Harvey D, Jack CR, Jagust W, Liu E, Morris JC, Petersen RC, Saykin AJ, Schmidt ME, Shaw L, Siuciak JA, Soares H, Toga AW, Trojanowski JQ; Alzheimer's Disease Neuroimaging Initiative: The Alzheimer's Disease Neuroimaging Initiative: a review of papers published since its inception. Alzheimers Dement 2012; 8(suppl):S1–S68 [Review]
15. Jack CR Jr, Vemuri P, Wiste HJ, Weigand SD, Aisen PS, Trojanowski JQ, Shaw LM, Bernstein MA, Petersen RC, Weiner MS, Knopman DS; Alzheimer's Disease Neuroimaging Initiative: Evidence for ordering of Alzheimer's disease biomarkers. Arch Neurol 2011; 68:1526–1535
16. Smith CD, Andersen AH, Gold BT. Structural brain alterations before mild cognitive impairment in ADNI: validation of volume loss in a predefined antero-temporal region. J Alzheimers Dis (Epub ahead of print, Mar 29, 2012)

17. Rosenberg PB, Mielke MM, Appleby BS, Oh ES, Geda YE, Lyketsos CG: The association of neuropsychiatric symptoms in MCI with incident dementia and Alzheimer disease. Am J Geriatr Psychiatry (Epub ahead of print, Apr 27, 2012)
18. Barnes DE, Yaffe K, Byers AL, McCormick M, Schaefer C, Whitmer RA: Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia. Arch Gen Psychiatry 2012; 69:493–498
19. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett DK, Bennett DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW, Seshadri S; American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia: Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011; 42:2672–2713

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