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Philip B. Gorelick and Farzaneh A. Sorond

Epidemiology of Cognitive Impairment and the Dementias

The Burden of Dementia Spectrum Disorders and Associated Comorbid and Demographic Features

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Behnam Sabayan, Kathryn A. Wyman-Chick, and Sanaz Sedaghat

Dementia spectrum disorders (DSDs) are a major cause of mortality and disability worldwide. DSDs encompass a large group of medical conditions that all ultimately lead to major functional and cognitive decline and disability. Demographic and comorbid conditions that are associated with DSDs have significant prognostic and preventive implications. In this article, we will discuss the global and regional burden of DSDs and cover key demographic and clinical conditions linked with DSDs. In the absence of disease-modifying treatments, the role of primary prevention has become more prominent. Implementation of preventive measures requires an understanding of predisposing and exacerbating factors.

Establishing a Diagnosis of Cognitive Impairment and Dementia

Office- and Bedside-based Screening for Cognitive Impairment and the Dementias: Which Tools to Use, Interpreting the Results, and What Are the Next Steps?

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David L. Nyenhuis and Jaclyn Reckow

Elderly patients and their families are concerned about the patients' cognitive abilities, and cognitive screening is an efficient diagnostic tool, as long as clinicians administer the screens in a standardized manner and interpret the screen results accurately. The following brief summary reviews commonly used screening instruments and provides information about how to interpret screening test results. It concludes by showing how cognitive screening fits into a four-step process (Education, Screening, Follow-up, and Referral) of how to respond to patients with cognitive concerns.

Formal Neuropsychological Testing: Test Batteries, Interpretation, and Added Value in Practice

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Victor A. Del Bene, Adam Gerstenecker, and Ronald M. Lazar

Neuropsychologists evaluate patients for cognitive decline and dementia, using validated psychometric tests, along with behavioral observation, record review, clinical interview, and information about psychological functioning, to evaluate brain-behavior relationships and aid in differential diagnosis and treatment planning. Also considered are premorbid functioning, education, sex, socioeconomic status, primary language, culture, and race-related health disparities when selecting tests, interpreting performance, and providing a diagnostic impression. Neuropsychologists

provide diagnostic clarity, explain symptoms and likely disease course to patients and family members, and assist the family with future planning, behavioral management strategies, and ways to mitigate caregiver burden.

Brain Networks, Clinical Manifestations, and Neuroimaging of Cognitive Disorders: The Role of Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), and Other Advanced Neuroimaging Tests 45

Borna Bonakdarpour and Clara Takarabe

In this article, we briefly discuss imaging modalities used in clinical settings for neuroanatomical characterization and for diagnosis of the underlying disease. We then discuss how each neuroimaging tool can be used in the context of clinical syndromes. The major underlying causes relevant to our discussion include Alzheimer disease, Lewy body disease, cerebrovascular disease, frontotemporal degeneration, autoimmune diseases, and systemic or metabolic derangements.

Blood and Cerebrospinal Fluid Biomarkers in Vascular Dementia and Alzheimer's Disease: A Brief Review 67

Philip B. Gorelick

The Maintenance of brain health is a lifelong process whereby potentially deleterious exposures such as cardiovascular risks, amyloid beta, and phosphorylated tau may adversely affect the brain decades before there are clinical manifestations. Thus, the early structural and neuropathological foundation for the development of cognitive impairment and its allied features later in life may provide precursor targets such that interventions may be applied to prevent or slow cognitively impairing processes if the underlying mechanism(s) can be addressed in time.

What Are the Key Diagnostic Cognitive Impairment and Dementia Subtypes and How to Integrate all of the Diagnostic Data to Establish a Diagnosis? 77

Sheena Baratono and Daniel Press

Diagnosis of dementia requires a detailed history, physical examination, imaging, and sometimes neuropsychological testing or ancillary tests. Mild cognitive impairment is defined as an objective impairment in cognitive performance but preserved ability to do activities of daily living. Dementia is diagnosed when impairment in activities of daily living develops. Common types of dementia covered here include mild cognitive impairment, Alzheimer's disease, Lewy body dementia, frontotemporal dementia including primary progressive aphasia, and vascular dementia.

Underlying Neuropathology and Basic Mechanisms

Neuropathology of the Common Forms of Dementia 91

Rupal I. Mehta and Julie A. Schneider

Dementias encompass a range of debilitating neurologic conditions. Here, we summarize the neuropathology of common forms of dementia, focusing on Alzheimer disease (AD) and related dementias. AD is part of a spectrum of neurodegenerative diseases that consists of various protein

inclusions (ie, proteinopathies) but other brain abnormalities are also related to dementia. Beta-amyloid and tau aggregates are hallmarks of AD. Other tissue substrates include Lewy bodies, TDP-43 inclusions, vascular brain lesions, and mixed pathologies. This review highlights the complexity of neurodegenerative and other disease substrates and summarizes topography of these lesions and concepts of mixed brain pathologies, resistance, and resilience.

Vascular and Nonvascular Mechanisms of Cognitive Impairment and Dementia 109

Betul Kara, Marcia N. Gordon, Mahsa Gifani, Anne M. Dorrance, and Scott E. Counts

Aging, familial gene mutations, and genetic, environmental, and modifiable lifestyle risk factors predispose individuals to cognitive impairment or dementia by influencing the efficacy of multiple, often interdependent cellular and molecular homeostatic pathways mediating neuronal, glial, and vascular integrity and, ultimately, cognitive status. This review summarizes data from foundational and recent breakthrough studies to highlight common and differential vascular and nonvascular pathogenic mechanisms underlying the progression of Alzheimer disease, vascular dementia, frontotemporal dementia, and dementia with Lewy bodies.

Prevention and Treatment of Common Forms of Cognitive Impairment and Dementia

The Role of Vascular Risk Factors in Cognitive Impairment and Dementia and Prospects for Prevention 123

Simin Mahinrad, Farzaneh Sorond, and Philip B. Gorelick

One of the most challenging clinical expressions of population aging is cognitive impairment and dementia. Among risk factors for the development of dementia, modifiable vascular risk factors have emerged as contributors to both vascular and nonvascular types of dementia. Epidemiologic studies have been particularly informative in understanding the link between vascular risks and dementia across the life course. We discuss vascular risks for dementia and cognitive impairment and practical management recommendations.

Treatment of Vascular and Neurodegenerative Forms of Cognitive Impairment and Dementias 135

Landon Perlett and Eric E. Smith

Ideally, dementia care should be provided by a collaborative team. Eligible patients should be treated with the cognitive-enhancing medications, the cholinesterase inhibitors and memantine. For most of the common causes of dementia, there are no disease-modifying medications, with the exception that vascular dementia can be prevented by treating vascular risk factors to prevent stroke. There is hope that Alzheimer disease can be treated by using monoclonal antibodies that target amyloid beta, although more trials are needed. Holistic, patient-centered care can enhance quality and extend the time that the patient can live safely in the community.

Brain Reserve, Resilience, and Cognitive Stimulation Across the Lifespan: How Do These Factors Influence Risk of Cognitive Impairment and the Dementias? 151

Farzaneh A. Sorond and Philip B. Gorelick

In the absence of effective treatments for dementia, maintaining cognitive health in old age is one of the major challenges facing aging societies. Interventions for cognitive health that are tailored to the person are more likely to bring the best benefits with a minimum burden. We review the existing literature on this topic and discuss the role of the primary care physician.

Beyond Memory and Other Cognitive Dysfunction: Neurobehavioral and Psychiatric Disorders

Diagnostic and Management Strategies for Common Neurobehavioral and Psychiatric Disturbances Among Patients with Cognitive Impairment and the Dementias 161

Akashleena Mallick and Alessandro Biffi

Neurobehavioral and neuropsychiatric symptoms are highly prevalent among individuals diagnosed with cognitive impairment or dementia and impact the quality of life for patients and caregivers alike. Diagnosis and management of these conditions (including primarily depression, anxiety, apathy, psychosis, agitation, and aggression) is crucial to optimal patient care outcomes in clinical practice. The present article provides a practical review of diagnostic approaches and management strategies for behavioral and neuropsychiatric disorders arising in patients with cognitive impairment, up to and including dementia.

Working Together Globally

Harmonizing Ethno-Regionally Diverse Datasets to Advance the Global Epidemiology of Dementia 177

Darren M. Lipnicki, Ben C.P. Lam, Louise Mewton, John D. Crawford, and Perminder S. Sachdev

Understanding dementia and cognitive impairment is a global effort needing data from multiple sources across diverse ethno-regional groups. Methodological heterogeneity means that these data often require harmonization to make them comparable before analysis. We discuss the benefits and challenges of harmonization, both retrospective and prospective, broadly and with a focus on data types that require particular sorts of approaches, including neuropsychological test scores and neuroimaging data. Throughout our discussion, we illustrate general principles and give examples of specific approaches in the context of contemporary research in dementia and cognitive impairment from around the world.