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Alzheimer's & Dementia

Perspective

Toward common mechanisms for risk factors in Alzheimer's syndrome

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Abstract The global strategic goal of reducing health care cost, especially the prospects for massive increases due to expanding markets for health care services demanded by aging populations and/or people with a wide range of chronic disorders-disabilities, is a complex and formidable challenge with many facets. Current projections predict marked increases in the demand for health driven by both the exponential climb in the prevalence of chronic disabilities and the increases in the absolute numbers of people in need of some form of health care. Thus, the looming predicament for the economics of health care systems worldwide mandates the formulation of a strategic goal to foster significant expansion of global R&D efforts to discover and develop wide-ranging interventions to delay and/or prevent the onset of chronic disabling conditions. The rationale for adopting such a tactical objective is based on the premise that the costs and prevalence of chronic disabling conditions will be reduced by half even if a modest delay of 5 years in the onset of disability is obtained by a highly focused multinational research initiative. Because of the recent history of many failures in drug trials, the central thesis of this paper is to argue for the exploration-adoption of novel mechanistic ideas, theories, and paradigms for developing wide range and/or types of interventions. Although the primary focus of our discussion has been on biological approaches to therapy, we recognize the importance of emerging knowledge on nonpharmacological interventions and their potential impact in reducing health care costs. Although we may not find a drug to cure or prevent dementia for a long time, research is starting to demonstrate the potential contributes of nonpharmacological interventions toward the economics of health care in terms of rehabilitation, promoting autonomy, and potential to delay institutionalization, thus promoting healthy aging and reductions in the cost of care.

Keywords: ■■■

1. Background

The global strategic goal of reducing health care cost, especially the prospects for massive increases due to expanding markets for health care services demanded by aging populations and/or people with a wide range of chronic disorders-disabilities, is a complex and formidable challenge with many facets. Current projections predict marked increases in the demand for health driven by both the exponential climb in the prevalence of chronic disabilities and the increases in the absolute numbers of people in need of some form of health care.

Thus, the looming predicament for the economics of health care systems worldwide mandates the formulation of a strategic goal to foster significant expansion of global R&D efforts to discover and develop wide-ranging

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interventions to delay and/or prevent the onset of chronic disabling conditions. The rationale for adopting such a tactical objective is based on the premise that the costs and prevalence of chronic disabling conditions will be reduced by half even if a modest delay of 5 years in the onset of disability is obtained by a highly focused multinational research initiative [1,2].

Because of the recent history of many failures in drug trials, the central thesis of this paper is to argue for the exploration-adoption of novel mechanistic ideas, theories, and paradigms for developing wide range and/or types of interventions. Although the primary focus of our discussion has been on biological approaches to therapy, we recognize the importance of emerging knowledge on nonpharmacological interventions and their potential impact in reducing health care costs. Although we may not find a drug to cure or prevent dementia for a long time, research is starting to demonstrate the potential contributes of nonpharmacological interventions toward the economics of health care in terms of rehabilitation, promoting autonomy, and potential to delay institutionalization, thus promoting healthy aging and reductions in the cost of care.

An international strategic research-planning workshop (The meeting was convened by the Network Center for Biomedical Research in Neurodegenerative Disease (CIBERNED), CIEN Foundation, and Reina Sofia Foundation, Madrid, Spain.) was organized on September 21–23, 2016 in Malaga, Spain to consider some forward-looking ideas for such an international cooperative research effort. The present paper outlines the challenges and recommendations for future research on a broad spectrum of interventions.

2. Why focus on Alzheimer?

Chronic brain disorders, such as Alzheimer's disease (AD), dementia, and other neurodegenerative disorders, constitute some of the most significant contributors to the quandary of health care systems worldwide. These neurological conditions that lead to prolonged functional impairments (i.e., diminish individuals' capacity to carry out activities of daily living) exemplify a unique class of disabilities because of their profound economic impact and psychosocial ramifications. Progressive functional impairments of cognition, motor skills, and effect, which are the most common clinical features of these unremitting brain conditions, ultimately lead to total reliance on labor-intense care to sustain life. AD has been proposed as the perfect prototype for this wide range of disorders and a pragmatic starting point (a proxy) for attacking the larger and more complex problem of chronic brain disorders [1,2].

Remarkable advances have been made in recent years in understanding the biological basis of neurodegeneration. Subsequently, it has become increasingly accepted that delaying the onset of disabling symptoms of neurodegenerative conditions is an attainable goal. Hence, developing R&D capacity for innovations that will reduce the prevalence of chronic brain disorders is an urgent need. However, several scientific impediments should be first surmounted. Among these barriers, crucial challenges are (1) changing current paradigms for the development of novel treatments and (2) improving the discovery of more effective therapeutic targets.

In the general arena of stimulating new thinking and fostering new perspectives, the important topics of modifiable risk factors and disease mechanism were the focus of discussion at the Malaga meeting. The present paper outlines the perspectives and recommendations of some key opinion leaders in the field of dementia research participating in the event. Here, we discuss some of the important obstacles to develop effective therapies as well as future direction for research and opportunities for therapy development.

3. New perspectives on risks factors and disease mechanisms

Alzheimer's syndrome is a polygenic and heterogeneous disorder with multiple patterns of expression. The late-onset sporadic form (SAD) is the most prevalent AD type, with the early-onset familial type (FAD) being responsible of only about 1% of the cases. Although both types follow a similar pathological and biochemical course, it is highly debated whether they should be considered as a single pathophysiological entity. Therefore, it would be of the highest importance to have a single general mechanistic hypothesis that could harmonize all biochemical and neuropathological features of both AD types.

In this context, a large part of the deliberations at Malaga were devoted to the pathogenic mechanisms underlying the neurodegenerative process. It has been a quarter of a century since the amyloid cascade hypothesis proposed that the presence of amyloid beta (Aβ) peptide aggregates is the first cause in the development of AD pathogenesis, whereas neurofibrillary pathology and neuronal cell loss are consequences of that primary cause [3]. Although FAD-based genetic evidence has provided strong support to the hypothesis, clinical trials targeting the amyloid pathway on SAD patients have shown disappointingly negative results in recent years, leading to discussions about whether the amyloid cascade hypothesis might not be valid for all SAD cases [4,5].

Discovery of mutations in the *APP*, *PSEN1*, and *PSEN2* genes causing FAD has been instrumental in the current understanding of the biochemical pathways leading to neurodegeneration and dementia. Furthermore, the findings from genome-wide association studies (GWASs) and massive parallel sequencing have come to underscore the multifactorial nature of AD. Notwithstanding, translating genetic findings into functional molecular mechanisms biologically relevant in disease pathogenesis and therapy design still remains a challenge.

On the other hand, several stages during disease progression have been proposed, with Aβ pathology developing