Introduction

Metabolic-Cognitive Syndrome: Metabolic Approach for the Management of Alzheimer's Disease Risk

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INTRODUCTION

Alzheimer's disease (AD) is the most frequent form of dementia in the elderly [1]. On the basis of future forecast, AD will have a tremendous impact on society and medical systems because dementia is the most important contributor to disability in the elderly [2]. The prevalence and incidence of dementia are relatively low in patients 60 to 65 years of age, but there is an exponential increase with age reaching almost 50% in those 85 years of age [3, 4]. After 90 years of age, the incidence of AD raises from 12.7% per year in the 90- to 94-year-old age group, to 21.2% per year in the 95- to 99-year-old age group, and to 40.7% per year in those at least 100 years old [5]. The progressive nature of AD, leading to severe functional and cognitive deterioration and increased comorbid disease, is one of the major determinants of institutionalization and mortality in the elderly [6, 7]. Consequently, the magnitude of this devastating disease has a significant impact on caregivers and healthcare systems.

At present, no effective treatments are available for prevention or cure of this devastating disease. Therefore, a growing burden of epidemiological data focused on risk factors [8]. Age and apolipoprotein E ε4 genotype are the most known AD risk factors [9], but they are not modifiable. Other possible risk factors for AD include female gender, ethnicity, family history of Down syndrome [9], maternal history of AD [10], education level (or cognitive reserve) [11], head trauma [12], and cerebrovascular risk factors [13]. Recently, great attention has been paid to the metabolic syndrome (MetS) [14] as a potential trigger of pathological molecular pathways dementia-linked. A strong and increasing body of evidence supports the association of MetS and metabolic determinants with cognitive impairment and dementia. In particular, MetS appeared to increase the risk for age-related cognitive decline, while for mild cognitive impairment (MCI) and its progression to dementia, the findings were too limited to draw any conclusion. Furthermore, the cumulative evidence did not suggest an association between MetS and the risk of developing overall dementia. On the contrary, several studies suggested that MetS may be linked to the risk of vascular dementia, while contrasting findings show a possible role of MetS in developing AD [14]. Moreover,

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it has been shown that MetS is also a risk factor for neurological disorders such as stroke and depression, as well as for dementia and AD [15]. Although molecular mechanisms underlying the mirror relationship between MetS and neurological disorders are not fully understood, it is becoming increasingly evident that all cellular and biochemical alterations observed in MetS (impairment of endothelial cell function, abnormality in essential fatty acid metabolism, and alterations in lipid mediators along with abnormal insulin/leptin signaling) may represent a pathological bridge between MetS and various neurological disorders.

The prevalence of obesity and MetS has increased over the past several decades and is expected to increase [16]. MetS is defined as a cluster of vascular and metabolic risk factors like visceral obesity, hypertension, dyslipidemia, and altered glycemic homeostasis [14]. Furthermore, it is characterized by an inflammatory cascade and release of several cytokines which act in several organs and systems, including the brain [17, 18]. These changes modulate immune response and inflammatory reaction that lead to alterations in the hypothalamic "bodyweight/appetite/satiety" set point, following the initiation and development of MetS. This condition is the result of a change in lifestyle of the affluent society, and MetS could be prevented by a particular attention and diffusion of a protective diet model in association with a personalized physical activity plan.

Besides the vascular features of MetS influencing AD onset, the most intriguing aspect not explored yet is the metabolic-hormonal alterations over the course of MetS that may be detrimental for neuronal cells. In fact, metabolism depends on the feedback between central neuronal structures and peripheral organs [19]. One of the aims of this Supplemental Issue was to recognize possible pathological mechanisms underlying the suggested epidemiological link between MetS and AD. Therefore, the relationships between each component of MetS and AD have been examined in depth, as well as an attempt to obtain a comprehensive outlook over the simple addition of single MetS components. Starting from the hypothesis that insulin-resistance (from which result all metabolic disturbances of MetS) could be involved in the neuropathological cascade of AD, we postulated the existence of a "metabolic-cognitive syndrome" (MCS) [20]. This term is not a clinical label but rather a pathophysiological model where we can now identify patients with MetS plus cognitive impairment of degenerative or vascular origin, helping us to better understand neuropsychological and neuropathological features of these predemen-

tia or dementia syndromes associated to MetS. The identification of a clinical profile of the MCS could be central in detecting in these patients a molecular profile of higher risk to develop predementia or dementia syndromes.

Another interesting aspect of this Supplemental Issue is the initial attempt to draw a common genetic background of both the pathological conditions, with the hope to stimulate further studies on this topic [21, 22]. A variety of strategies have been used to identify genes influencing AD onset. Until recently, most reports came from linkage analysis and from studies that have examined the association of single-nucleotide polymorphisms. Thanks to the completion of the Human Genome Project, the development of public databases and advances in high-throughput, high-density genotyping technology, our knowledge is increased. Indeed, genome-wide association studies have emerged as an increasingly effective tool for identifying genetic contributions to complex diseases and represent the next frontier for furthering our understanding of the underlying etiologic, biological, and pathologic mechanisms associated with chronic complex disorders [23].

However, many issues are still unsolved. First of all, there is the doubt as to whether amyloid-β (Aβ) and hyperphosphorylated tau protein are causal in neurodegenerative damage or are the tip of the iceberg of other underlying mechanisms of neurodegeneration. Moreover, these neuropathological hallmarks of AD may represent even a cellular attempt of response to any kind of neuronal insult (e.g., vascular, ischemic, or oxidative). If the latter hypothesis were true, drugs targeting Aβ could be detrimental for AD patients. In fact, in the last 15 years, most of the efforts of the pharmaceutical industry in AD have been directed against the production and accumulation of Aβ [24]. Unfortunately, these efforts have not produced, up to now, effective therapies, given that the exact mechanisms leading to AD are largely unknown, thereby limiting the identification of effective disease-modifying therapies. Converging evidence from both genetic at-risk cohorts and clinically normal older individuals suggests that the pathophysiological process of AD begins years, if not decades, before the diagnosis of clinical dementia [25]. Probably, it is mandatory to start earlier with a potential AD treatment in order to counteract the disease progression. The recent introduction of new diagnostic criteria of AD based on specific cognitive patterns and reliable biomarkers [26] may open a new paradigm of therapeutic intervention based on the distinction of two preclinical states of AD in

which individuals are free of cognitive symptoms. One group is formed of 'asymptomatic subjects at risk for AD' with biomarker evidence of AD pathology. The other group is formed of 'presymptomatic AD subjects' carrying genetic determinants, which eventually will develop the disease [27]. New drugs should be tested in these two populations of 'asymptomatic' or 'presymptomatic' subjects rather than in AD patients. Very recently, the National Institute on Aging and the Alzheimer's Association charged a workgroup with the task of revising the 1984 criteria for AD dementia [28], developing criteria for the symptomatic predementia phase of AD (MCI due to AD) [29] and defining the preclinical stages of AD for research purposes and toward earlier intervention at a stage of AD when some disease-modifying therapies may be most efficacious. New and promising drugs are still under investigation, but at this time, according to the latest discoveries, it is necessary to synthesize new and old concepts, looking at this disease in a more comprehensive manner. In this way, a more accurate clinical selection of subjects at high-risk to develop AD who would successfully benefit from these upcoming treatments would be possible. In fact, selecting patients only on the basis of well-known risk factors seems to be inadequate in light of new knowledge. Therefore, as tumor markers are useful for follow-up rather than diagnosis, similarly, we believe that screening of subjects for plasma or cerebrospinal fluid biomarkers would not be sufficient for an early diagnosis of AD. Given that the onset of this disease is probably the result of interaction among genetic and environmental factors, we are aware that the research agenda should consider new platforms of study, going beyond the monolithic outlook of AD, with the synthesis of epidemiological, experimental, and biological data, under a unique pathophysiological model as a point of reference for further advances in the field.

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