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Commentary on “A roadmap for the prevention of dementia II. Leon Thal Symposium 2008.” Subjective cognitive impairment as an antecedent of Alzheimer’s dementia: policy import

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It is becoming increasingly evident that the process of Alzheimer’s disease (AD), which is known to be gradual and continuous, begins many years, indeed, decades before symptoms of dementia become evident. Dementia is defined as a condition in which the cognitive deficits must be sufficiently severe to cause impairment in occupational and social functioning [1]. The physiologic mechanisms eventuating in dementia and AD may begin very early in life [2–4]. Similarly, pathologic hallmarks of AD appear to develop decades before the dementia of AD becomes manifest. For example, Braak and Braak report that in a consecutive series of 2,369 unselected autopsy cases, approximately 50% of subjects who died between age 50 and 55 manifested the neurofibrillary pathology of AD [5].

In terms of the behaviorally manifest process of the development and course of AD, more than two decades ago, we described seven major stages in the evolution of the brain aging and progressive dementia process of AD. These descriptions, in the form of the Global Deterioration Scale (GDS) [6] and related measures [7,8], had an immediate impact on the medical community [9] and lay-persons [10], as well as the research community. However, the meaning and implications of these stages for the medical and scientific communities and for the research agenda are continuing to evolve, and, in fact, are acquiring a new sense of urgency.

One of the stages described in the GDS, stage 3, is a stage prior to the development of overt dementia, in which deficits become subtly evident, for example in the context of a detailed clinical interview or in demanding employment settings. In 1988 we published cross-sectional findings, which indicated diverse deficits in psychometric test performance for persons at this GDS 3 stage, in comparison with that of persons in earlier stages [11]. On the basis of these findings, we suggested the terminology “mild cognitive impairment,” to describe persons at this GDS 3 stage [11]. Subsequently, in longitudinal studies: (1) we verified the relative morbidity of the GDS 3 stage of mild cognitive impairment (MCI) in comparison with earlier stages [12], and (2) we prospectively confirmed earlier estimates [13] that this stage of MCI lasts approximately 7 years in otherwise healthy older persons prior to the advent of overt dementia pathology [14]. Changes in MCI subjects in comparison with both persons at earlier GDS stages and in comparison with persons with mild or more severe dementia in terms of

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diverse aspects, including motor changes, neurologic reflex changes, and diverse neuroimaging assessments, were extensively described in the literature (see Reisberg, et al., 2008 [15], for a review). In recent years, Petersen and colleagues have somewhat modified our descriptions of MCI and, working with various groups, enhanced the recognition and worldwide understanding of this pre-dementia condition [16–19]. As a prodromal, identifiable condition, prior to the advent of the overt dementia of AD, the recognition of MCI greatly extends the epidemiologic, social, and economic dimensions of the evolving pathology of AD.

The GDS also identifies a stage prior to MCI in which older persons develop subjective complaints of cognitive impairment (SCI, GDS stage 2). More than two decades ago, we hypothesized that this SCI stage precedes MCI in the course of the development of AD, and lasts approximately 15 years before MCI symptoms become manifest [13]. Because the mild cognitive impairment stage lasts ~ 7 years prior to mild AD, an understanding and recognition of the nature and import of MCI was essential before the SCI stage could be elucidated. Recent studies are identifying physiologic differences between SCI subjects and age-matched no cognitive impairment [NCI] (GDS stage 1) persons in physiologic parameters including brain metabolism [20] and cortisol levels [21]. Prognostic markers of the development of subsequent mild cognitive impairment in persons with SCI are also being identified, for example using electrophysiologic markers [22]. These studies have supported the earlier estimates of the duration of the SCI stage as being approximately 15 years prior to the advent of MCI [13,22, 23]. Importantly, current studies are also showing evidence of quantifiable cognitive deficits accompanying these SCI symptoms. For example, subjects with SCI were recently observed to score more than a half-point lower on average on the mini-mental status examination [24], than an NCI cohort [25]. However, the SCI subjects, despite poorer cognitive performance on average than similarly aged NCI persons, continue to score well within the normal range on psychological and other test measures. Consequently, the import for society of the observable performance decrements in this pre-MCI stage, for example in terms of decreased occupational performance, if any, remains to be determined.

It is clear from current epidemiologic studies that SCI symptoms become very common as persons age. These symptoms occur in approximately a quarter to a half of all persons in the community aged 65 or greater [26–29]. It is also clear that these SCI symptoms are very troubling to many older persons. Over the past 30 years, approximately a third of persons presenting to our aging and dementia research center have come because of these SCI symptoms. Also, these subjective complaints of impairment appear to be a major reason for older persons taking a variety of prescription and non-prescription treatments, including off-label medications approved for dementia, or other conditions, and non-prescription vitamins and nutraceuticals [30]. Hence, the economic consequences of the SCI symptoms in many older persons are clearly large in terms of societal costs.

Summary and Recommendations

The increasing recognition of this SCI stage as a prodromal condition eventuating in AD is of great importance in terms of the dimensions of AD. For example, if AD begins clinically at this SCI stage then AD can and should be viewed as affecting in an incipient, but overt form, between 9 and 19 million persons aged 65 or older in the United States population (i.e., 25 to 50% of the 12.4% of the U.S. population ≥ 65 years), as well as many persons at earlier ages [31]. These persons with SCI in the community are not presently counted in the AD population estimates. Therefore, the epidemiologic dimensions of AD including SCI may be approximately 3 to 5 times greater in the United States than previously recognized. Clearly, in the interest both of treating perceived morbidity and the eventual enormous consequences of AD as it evolves, the disease needs to be addressed at this formative SCI stage. How can these current opportunities be addressed appropriately? Two major suggestions are forwarded below.

1. Studies of AD prevention and SCI treatment need to be undertaken

The budget for AD research should be increased proportionately to the increased epidemiologic dimensions of the SCI problem, i.e., by a factor of 3 to 5 times the present budget. To achieve this logical and appropriate goal, the recommendation from the 2008 Leon Thal Symposium is endorsed that a business model be developed, outlining present costs, as well as the potential opportunities from the results of research assisting in the delay and prevention of eventual AD.

2. Medications that delay and prevent eventual AD in the SCI stage need to be developed

For various reasons, including proven safety and the cost savings from working with existing agents, the presently available pharmacopeia should be studied towards these ends. In terms of enhancing the financial incentives for such studies, it is suggested that the value of use patents based, in part, on medications previously approved for other indications, might be legislatively enhanced in various simply instituted ways. For example, it could be mandated that any prescribing for persons over a certain age fall within the domain of the use patent. Also, mandatory diagnostic coding for SCI, MCI and AD, which could be enforced analogously to the mandatory diagnostic coding which has been successfully applied to other medical conditions, would make use patents valuable.

With respect to the value and importance of use patents, it should be noted that some of the current medications approved for the treatment of AD were developed in initial approvals from medications on which use patents had been obtained for previously existing compounds. For example memantine, an agent originally patented by the Ely Lilly company in 1963 [32], was subsequently independently developed by the Merz company with a use patent, as the first (and, at this time, only) NMDA receptor antagonist treatment for AD. The United States approval for memantine for AD treatment came in 2003 on the basis of studies published from 1999 to 2004. Memantine became available in the United States market for the first time in 2004, more than 40 years after the initial patent filing. This is more than twice the lifespan of an enforceable and commercially viable initial patent application.

Conclusion

Recent work is pointing towards overt antecedents of eventual AD which affect a substantial proportion of persons over age 65. These findings indicate that AD may be profitably addressed at much earlier points in the development of the condition. The implications of these increased dimensions of AD and associated opportunities, costs and solutions can be addressed at the present juncture.

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