Perspectives

Diagnosis of Alzheimer’s disease: Two decades of progress*

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Abstract
A retrospective view of the critical events and advances in the development of criteria, instruments and algorithms in the diagnosis of Alzheimer’s disease. The review is from the vantage point of the National Institute on Aging and its role in the development of the national infrastructure, in the US, for clinical research on dementia. The paper discusses future research needs and challenges for developing new diagnostic armamentarium for early and accurate detection of neurodegenerative processes of dementia in the early prodromal stages or during early mild cognitive impairments. © 2005 The Alzheimer’s Association. All rights reserved.

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1. Introduction

The 1985 article in the Archives of Neurology, “Diagnosis of Alzheimer’s Disease” [1] represents a small chapter in the prolonged efforts to characterize the distinct clinical–pathologic features of Alzheimer’s disease (AD). Although the study of dementia has a 100-year history, the attempts to address systematically the array of scientific and clinical issues related to differential diagnosis is a relatively recent phenomenon. This report is an account of the early history of the struggles to define the disease and the more recent efforts at the National Institute on Aging (NIA)/National Institutes of Health (NIH) to establish diagnostic criteria, standardized clinical assessment algorithms, and validated screening instruments and/or biological markers.

2. Early history

Although various forms of dementia have always been part of the human experience, the efforts for systematic description of the clinical–pathologic characteristics of the phenomenon gained traction in the late 1890s roughly paralleling advances in histology (chemistry of tissue stains), light microscopy, neuroanatomy, and other areas of biology [2, 3]. The early pioneers of the field were able to make some groundbreaking observations about dementia because of access to a wealth of new technologies for studying the brain and the emergence of vibrant academic environments that fostered interactions and cross fertilization among psychiatrist, neurologist, and neuropathologist. Reports by Blocq and Marinesco [1892] and later by Redlich [1898] began to describe the relationships between neocortical senile plaques and senile dementia. Oskar Fisher [1907] was one of the first to suggest that severity of dementia and memory loss might be associated with senile plaques. Alois Alzheimer, a psychiatrist with an abiding interest to “help psychiatry through the microscope,” was among the first to exploit the newly emerging tools for histologic study of the human brain. The 1907 report by Alois Alzheimer became the index case for “Alzheimer’s Disease”; however, the term did not receive broad endorsement until the eighth edition of Emil Kraepelin’s Textbook of Psychiatry published in 1910.

Nearly a century later, Alzheimer’s original report remains a crucial milestone in the annals of dementia research. The study approach, by Alzheimer, of combining meticulous clinical observations with systematic neuro-pathologic analysis of brain lesions become the template for NIA’s: (a) strategy to develop its extramural program of research support for Alzheimer’s disease and (b) program priority for promoting further interdisciplinary research on
the causal relationships between the clinical–pathologic phenotypes of dementia.

In the era between Alzheimer’s initial report and the 1960s, the primary focus of the scholarship on dementia was the epistemology of the disease and the struggle for consensus on the clinical definitions. Progress in understanding the relationships between the behavioral expression and pathologic phenotypes of dementia was relatively slow in this stage because of 2 impediments: first, the lack of validated standardized objective clinical assessment tools and, second, uncertainty in the definition of the clinical phenomenon.

During the 2 decades after WWII, arguably the start of the modern era of AD research, the question of whether AD changes were simply an accentuation of normal senescence, gradually began to emerge as a central research question. The important clinical controversy revolved around the issue of whether “presenile” and “senile” dementias were the same disorder. Newton in 1948 and later Neuman and Cohn in 1953 suggested that these 2 forms of the disease were identical. The challenge of distinguishing brain changes owing to pathology from those alterations as a result of healthy aging were started in a number of landmark investigations by Blessed, Tomlinson, and Roth in the mid 1960s [4]. However, the dispute could not be settled without comparisons of the clinical/biological/neuropathologic phenotypes of the disease. Such comparisons became possible in the early 1960s with the introduction of the electron microscope (EM) as a research tool and the development of quantitative measures of dementia.

In 1963, Terry (in the US) and Kidd (in the UK) independently reported the findings of EM studies that showed the ultrastructure of a single neurofibrillary tangle to contain masses of microscopic fibers with periodic structure: paired helical filaments (PHF). These landmark studies enabled the field to: (1) develop quantitative assessments of the hallmark lesions, (2) clearly delineate the ultrastructure of the amyloid core (neuritic plaque), (3) develop methods of isolating plaques, neurofibrillary tangles, and preparation of enriched PHFs, and (4) set the stage for the discovery of more sophisticated molecular and immunologic probes to further characterize the abnormal proteins associated with the disease. Thus, these early ultrastructural studies by Terry, Kidd, and colleagues opened the door for more detailed molecular characterization of the 2 fibrous proteins and set the stage for the remarkable advances of the last few years in understanding the molecular neurobiology of AD.

The need for functional measures of severity and objective/quantitative tools to assess mental status was the crucial hurdle for progress in clinical/behavioral studies of this period. This problem was surmounted in 1968, with the publication of the Blessed, Tomlinson, and Roth Dementia Scale (Information-Memory-Concentration Test). This was an informant-based scale of memory function, orientation, information, concentration, and activities of daily living. The landmark prospective studies of this group for the first time correlated quantitative measures of dementia (cognitive and functional impairments) with estimates of the number of lesions (plaques), and the volume of brain destroyed by infarcts. These efforts to quantify the relationships between the clinical and biological indices of the disease established the foundation for subsequent program initiatives and several collaborative multisite longitudinal studies launched by NIA. In the mid 1960 to mid 1980 period, 4 categories of objective clinical measurement tools were developed and validated, some in longitudinal studies with autopsy confirmations. These include Mental Status Exams (eg, Dementia Scale or ICM Test, 1968; Mini-Mental Status Exam, 1975 [5]; Short Blessed Test, 1983), Global Measures of Dementia Severity (eg, Clinical Dementia Rating, 1993; Global Deterioration Scale, 1982; CAMDEX, 1986), Behavioral Scales (Geriatric Depression Scale, 1988; Agitation Inventory, 1986; CERAD Behavioral Rating Scale for Dementia, 1995; Clinical Impression of Global Change or CIBIC), and Cognitive Assessment Batteries (eg, Alzheimer Disease Assessment Scale or ADAS-cog) [6]. The efforts to construct quantitative measures of cognition and the validation of instruments for objective evaluation of symptoms were critical to the refinements in the characterization of the disease. These advances in assessment of the severity of the disease became the foundation for much of the current “routine clinical-workup” and set the “standard” for clinical staging methods, an essential element of clinical research.

Although many investigators were laboring to develop objective measures for assessing the severity of symptoms, the uncertainty about the clinical “identity” of Alzheimer’s diseases lingered until the 1976 editorial by Katzman [7]. This landmark report for the first time framed Alzheimer’s disease as an important public health/medical issue. The Katzman editorial was an important step toward: (a) the recognition of a need for specific diagnostic criteria and (b) reviving the argument for a common cause for late-onset and presenile dementia, an earlier thesis suggested by Newton [1948] and by Neuman and Cohn [1953].

3. Recent history: NIA initiatives on “Diagnosis of Alzheimer’s Disease”

The recent history of efforts to improve the diagnostic armamentarium, particularly the impact of the 1985 article “Diagnosis of Alzheimer’s Disease,” becomes meaningful only in the context of the overall struggles to establish the neurobiology of disease program at the NIA.

The Institute was established in 1974 with an amorphous congressional authorization to address the problems and diseases of the aged. But, the NIA’s implicit directive was to develop and support interdisciplinary research on healthy (normal) aging as well as disorders of aging. In 1977, this author was recruited to translate the Institute’s broad legis-
The series of “Research Planning Workshops” organized by NIA since 1978, were designed primarily to solicit advice from the extramural scientific community. These planning workshops were an essential tool for identifying gaps in knowledge and formulating strategies concerning new program directions. Also, they served as a critical vehicle for establishing collaborating network of clinical investigators and creating the infrastructure necessary to developing standardized diagnostic procedures. The 1985 Archives of Neurology report, which was based on the proceedings of one such “Research Planning Workshop on Diagnosis of Alzheimer’s Disease,” was organized in December 1983. The recommendations of this workshop led to several NIA initiatives in subsequent years and set the stage for some of today’s “hot topics.” The neuropathology panel of this workshop took the first step toward defining the minimum microscopic criteria necessary for histologic diagnosis of AD. The neurology panel suggested that the term Alzheimer Disease be reserved for patients who show a compatible clinical course along with the histopathologic and neuro-chemical changes associated with the disease. The panel also considered the problem of distinguishing AD from benign senescent forgetfulness (mild cognitive impairment [MCI]) and non-Alzheimer–type dementia. Other topics and recommendations of this workshop included neuroimaging, biomarkers, molecular genetics, longitudinal studies, brain banks, establishment of family registries and pedigree studies, animal models, and the need for research on normal brain aging.

Before 1984, in the absence of specific diagnostic criteria for Alzheimer, the DSM-III criteria for diagnosis of dementia had fulfilled the requirements of clinical research [8]. Finally, this need was addressed with the publications of (a) “Diagnosis of Alzheimer’s Disease,” [1] and (b) “NINCDS-Alzheimer’s Disease and Related Disorders Association (ADRSA) Diagnostic Criteria” [9], which specified inclusion– exclusion factors and 3 levels of confidence: probable, possible, and definite (requiring histopathologic confirmation). Since the publication of these articles, substantial progress has been made in the accuracy, reliability, sensitivity, and sophistication of diagnostic assessment instruments and algorithms. Some of the most significant contributions to current clinical knowledge on diagnosis stemmed from the early efforts to (a) refine the clinical description of the phenomenon/symptoms, (b) establish clinical–pathologic correlations, (c) develop objective measures of behavior–psychometric assessment instrument, (d) establish diagnostic criteria and standardize diagnostic procedures, (e) establish infrastructure for longitudinal clinical–pathologic studies and the remarkable advances in understanding the neurobiology of dementia during the last 3 decades.

One of the earliest NIA initiatives to expand research on diagnosis and treatments focused on promoting the construction and validation of assessment tools specifically designed for cognitive changes in several domains. The best know example of this was the proposal funded in 1978 that resulted in the development of the Alzheimer’s disease Assessment Scale (ADAS) published in 1984 [6]. Other strategies were required to address issues in the develop-
ment of diagnostic criteria, standardization of assessment tools, and the methodologies of clinical trials. Thus, the mid 1980s was a watershed period for Alzheimer’s research in general but in particular for improvements in the technologies for diagnosis. In 1984, several concurrent developments enabled multisite collaborative clinical studies. These included (a) Alzheimer’s Disease Centers provided necessary research infrastructure, (b) standardized cognitive assessment instruments and global measurement of dementia severity were introduced (ADAS, CDR, CIBIC), (c) NINCDS-ADRDA criteria provided a systematic clinical diagnostic system supporting comparisons across centers, (d) Glenner and Wong identified amyloid, (e) Consortium to Establish Registries for Alzheimer’s disease (CERAD) (1987), and (f) Alzheimer’s Disease Cooperative Study (ADCS) was established (1991).

Once the challenges of developing diagnostic criteria and objective assessment instruments were overcome, the next major impediment for clinical research was the effort to (1) validate the diagnostic criteria with histopathologic confirmations, thus, the need for neuropathologic criteria; (2) standardize (reliability, sensitivity, specificity) various clinical assessment instruments; and 3) construct new measurements for changes in behaviors, symptoms of various domains of cognition. The availability of standardized, well-validated quantitative assessment instruments were indispensable prerequisites for NIA’s subsequent initiatives (eg, Centers Program; CERAD; ADCS; Alzheimer’s Disease Neuroimaging Initiative [ADNI]).

To address the long-term strategic goal of developing treatments, it was necessary for NIA to build (a) mechanisms for promoting collaborative research, (b) the capability of the field to conduct longitudinal clinical research and clinical trials, and (c) infrastructure for clinical research. The NIA began to create the necessary national research infrastructure.

The Alzheimer’s Disease Research Centers (ADRCs), established in 1984 and the Alzheimer’s Disease Core Centers (ADCCs), established in 1990, were central components of the research and capability infrastructure. These programs, referred to as the Alzheimer’s Disease Centers or ADcs, provide the infrastructure for integrating clinical and basic science research and allowed the augmentation of a wide range of studies on the etiology and pathogenesis of AD. In 1991 the “Satellite Clinics” program was established to fund outreach to underserved or rural patient groups. Now satellites are an integral part of many ADCs.

The Alzheimer’s Disease Patient Registry Program (ADPR) was launched in 1986 to address the goal of developing standardized diagnostic assessments. This program included the Consortium to Establish a Registry for AD (CERAD) led by Al Heyman and Gerda Fillenbaum, the Mayo Clinic Registry led by Len Kurland and Ron Peterson, the Seattle site led by Eric Larson, the Mon Valley Project with Lewis Kuller and Mary Ganguli, and Denis Evans’s group in East Boston. The CERAD project was successful in establishing uniform methods for the diagnosis and assessment of AD because of the dedicated and effective leadership provided by Al Heyman and the cooperation of clinicians and investigators nation and worldwide. The ADPR program overall was instrumental in the development of assessment instruments and procedures and also in filling gaps in the epidemiology of AD [10, 11].

During the following 2 decades the improvements in the accuracy of the clinical diagnosis were remarkable. The procedures for clinical assessment advanced steadily toward well-validated algorithms for identification of positive clinical phenotypes of the diseases. Early diagnosis has become one of the most important clinical accomplishments with profound implications for (1) research, (2) establishing the prevalence of AD, (3) initiating treatment when it may have optimal benefit, and (4) understanding the pathobiology of the disease. For example, the original cholinergic hypothesis was based on neuropathologic material from end-stage AD patients. Now that AD is diagnosed earlier, some investigators (eg, Ken Davis and Steve DeKosky) have suggested that simple cholinergic hypofunction may not be a feature of the initial stages.

The introduction of the concept of MCI as a potential precursor or prodrome of the disease was another significant milestone [11]. Several groups (eg, Barry Reisberg, Steve Ferris and the NYU group, Thomas Crook at NIMH, Ron Petersen and the Mayo Clinic group, Marilyn Albert and the MGH group, and John Morris and the Washington University group) contributed to efforts to improve the definitions and algorithms for distinguishing the early stages, MCI, from nondemented aging and in characterizing border zone conditions.

The notion of prodromal stages of the disease energized the current explorations for early biomarkers. Advances in molecular neurobiology and emerging imaging technologies promise to provide much-needed surrogate markers to detect and/or monitor progression during the early clinically asymptomatic stages. The classification of degenerative dementias is moving rapidly, not just toward diagnostic and prognostic biomarkers, but toward antecedent biomarkers, a system of categorization based on combined behavioral and protein abnormalities (eg, amyloidopathy, tauopathies, synucleinopathies, and prior protein disorders). The potential value of an amyloid imaging compound (Pittsburgh Compound) for early diagnosis was demonstrated recently by Bill Klunk and Chet Mathis (Pittsburgh), Henry Engler (Stockholm), and collaborators from Uppsala and Boston with their success in imagining Aβ-containing lesions in the living human brain.

The prospects that validated molecular and biochemical markers may soon complement clinical approaches in making early and valid diagnoses are very good [12]. However, any potential biomarker must detect a fundamental biological feature of the disease and be validated in neuropatho-
logic-confirmed cases before routine clinical use. Currently, none of the many (proposed) putative biomarkers have been validated in adequately powered investigations. Recent advances in neuroimaging technologies (eg, Pittsburgh Compound with PET) offer the potential to detect and follow longitudinally the clinical course of the disease. In the future, it might be possible for neuroimaging technologies, perhaps magnetic resonance imaging, to allow more direct monitoring of some biological phenotypes of the disease (eg, brain metabolic changes, Aβ, Tau, synapse loss or cell death via positron-emission tomography (PET), and other structural changes). In contrast to neuropsychological measurements, imaging measurements, when validated, will allow the more proximal brain changes associated with disease progression to be followed over time.

There is a general consensus that many of the advances in diagnosis, treatment(s), care, and understanding the cause(s) would not have been possible without the creation of instruments, criteria, infrastructure, and programs that support interdisciplinary research. Some of the spectacular clinical and research strides attributable in some measure to the NIA initiatives include:

- improvements in antimortem and postmortem diagnosis
- access to samples of blood, DNA, cerebrospinal fluid, and postmortem tissues from well-characterized patients for basic and clinical research
- advances in understanding the neurobiology of the normal aging brain as well as the mechanisms of AD and related neurodegenerative diseases
- capacity to pool data on large cohorts of research participants through the NACC, for example, the landmark cooperative study assessing the diagnostic impact of the APOE ε4 allele in the evaluation of dementia patients
- insights into the role of immune mechanisms, the complement cascade, proteases, glia, and head trauma in the pathogenesis of demnetic disorders
- benefits of NIA’s “team science” are reflected in the sharing of data and samples fostered by the Alzheimer’s Disease Centers network, Alzheimer Disease Cooperative Study and the National Alzheimer Disease Coordinating Center and the productivity of these groups

4. Prospects for the future

- Twenty years ago, ideas about “cure” and “prevention” were unconceivable; such things as diagnostic criteria, standardized assessment instruments, cadres of specialized professionals, memory disorder clinics, family support groups, or outreach programs, all taken for granted now, were not fully developed.
- Fifteen years ago, the knowledge on biological underpinnings and the genes associated with the disease had not been identified.
- Ten years ago, animal models of the disease were not available.
- Five years ago, persons’ risk for the disease could not be identified, and the concept of clinical trials to delay the symptoms was unconceivable.
- Until 2004, the Aβ protein, hallmark of the disease, could not be directly visualized in patients.
- Today, the field is on the brink of major breakthroughs that may lead to more effective treatments and, ultimately, to prevention. A great deal has been learned about the pathogenesis of neurodegeneration after less than 3 decades. Novel intervention strategies are being developed to ameliorate the neurotoxicity caused by abnormal metabolic products and prevent processes that lead to cell death. A large number of clinical trials are underway, both industry- and government (NIA-ADCS)-sponsored studies, with widely used drugs (eg, antioxidants, antiinflammatory agents, statins, vitamins, and folate) that might reduce the risk of Alzheimer’s disease. Intensive studies are underway on multiple fronts, from basic science to genetics to drug therapy to care giving. Recent public policy initiatives on disease prevention and the gradual shift of emphasis in drug discovery research, toward disease modification, have underscored the need for validated surrogate markers of AD. However, the major impediment to prevention or interventions to slow disease progression remains lack of a positive and validated marker or the technology for early and accurate detection of the prodromal neurodegenerative processes. The recently launched NIA ADNI is the much-needed strategy to address this critical need.
- The remarkable progress toward understanding AD and the improved prospect of discovering disease-modifying therapies will not have been possible without the (1) worldwide network of investigators working closely and collaboratively, (2) research infrastructure established by NIA and, (3) successful partnership between the NIA Alzheimer’s Association. Now these partnerships need to be expanded to include industry, foundations, and individual philanthropists. The goal for such a public–private working partnership is to mobilize all the necessary international resources for a new initiative to discovery
(and/or development) of interventions to prevent the disease. Time is running out; the epidemic of AD will completely overwhelm the health care system because of the substantial growth the numbers of people with AD. The demographic changes, resulting from the continuing increases in the life expectancy of the oldest-old, are going to have their full impact 20 to 30 years from now. The projected costs in human suffering and lost opportunities will be incalculable and unthinkable.

References