The Differential Diagnosis of Alzheimer’s Disease: Conceptual and Methodological Issues

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ABSTRACT: The study of Alzheimer’s disease is hampered by insufficient knowledge of its cause. It can best be described as a syndrome whose clinical and pathological features, and their associations over time, need to be more carefully examined. Issues which impede our understanding of this syndrome include the lack of: (a) a singular “gold standard” for its identification; (b) longitudinal studies with appropriate comparison groups and neuropathological follow-up; and (c) standardized multifaceted clinical assessment procedures. Our awareness of the significance of these issues has led us to undertake a large-scale prospective, longitudinal investigation of 399 dementing and normal individuals at Sunnybrook Medical Centre. As a result of problems identified, it is proposed that research efforts across various Canadian centres be coordinated to best utilize available resources and expertise.

RESUME: Le diagnostic différentiel de la maladie d’Alzheimer: problèmes conceptuels et méthodologiques. L’étude de la maladie d’Alzheimer est entravée par le manque de connaissances sur sa cause. Au mieux c’est un syndrome dont les manifestations cliniques et pathologiques et leur association dans le temps, doivent être étudiées plus attentivement. Les questions qui gênent notre compréhension de ce syndrome comprennent l’absence de: a) un standard unique (“étalon or”) d’identification de la maladie; b) des études longitudinales avec groupes témoins appropriés et suivi neuropathologique; c) un protocole d’évaluation clinique standardisé, à multiples volets. Notre prise de conscience de l’importance de ces problèmes nous a amenés à entreprendre une étude longitudinale prospective d’envergure, impliquant l’investigation de 399 sujets dément et normaux, au Centre Médical Sunnybrook. A la suite de l’identification de certains problèmes, nous proposons qu’il y ait une coordination des divers projets de recherche à travers le Canada afin d’utiliser de façon optimale les ressources et l’expertise disponibles.

pathological confirmation and a neuropathological diagnosis requires clinical confirmation. This problem arises because, as with the clinical criteria, there are no specific neuropathological markers for Alzheimer’s syndrome. The brain pathologies considered characteristic of Alzheimer’s disease may also appear in the brains of nondemented elderly individuals. Thus, there is a demonstrated need to direct research efforts at a better understanding of the relationship between clinical and neuropathological indices. 

Reliance on the false assumption that neuropathological findings provide the “gold standard” for the disease will only retard our progress in the understanding of this syndrome.

The next section of this paper will describe research strategies which, if employed, should lead to a more complete description of the syndrome and ultimately to a better understanding of it.

Sample size Because Alzheimer’s is a progressively deteriorating condition and may result in individual variation in expression, large samples of individuals who meet the existing diagnostic criteria must be followed. This is necessary in order to determine whether there are common clinical features consistent across these individuals yet distinct from both normal aging and other dementing processes. Unfortunately, sample sizes have typically been too small to identify the differential patterns unique to Alzheimer’s disease.

Comparison groups In order to establish the distinguishing characteristics of Alzheimer’s disease at both the neuropathological and clinical levels, comparisons must be made among individuals with diagnoses of Alzheimer’s disease, diagnoses of dementias of other etiologies, as well as normals. The majority of studies examining the distinguishing characteristics of Alzheimer’s disease have focussed on differences between the latter and normals. 

Unfortunately, with few exceptions, those studies comparing Alzheimer’s with other dementias have only used small samples. Because of these shortcomings, the value of the various measures in differentiating between Alzheimer’s disease and other forms of dementia remains to be established. The latter distinction is crucial if we are to progress to the stage of developing specific markers for the disease.

Another important rationale for the inclusion of individuals with dementias of different etiologies in the study sample is that it permits a comparison of the neuropathological features of these different groups. An illustration of the importance of such comparisons may be found in the research investigating subcortical dementias. Researchers examining the brains of individuals with Parkinsonian Lewy bodies have reported the presence of pathological changes characteristic of Alzheimer’s in many of these brains. 

Speculations regarding a common etiology for Alzheimer’s disease have focussed on differences between the latter and normals. Unfortunately, with few exceptions, those studies comparing Alzheimer’s with other dementias have only used small samples. Because of these shortcomings, the value of the various measures in differentiating between Alzheimer’s disease and other forms of dementia remains to be established. The latter distinction is crucial if we are to progress to the stage of developing specific markers for the disease.

Research design Until recently, retrospective cross-sectional designs have represented the majority of studies of Alzheimer’s disease. Typically, individual cases are selected on the basis of previously obtained documentation. The primary limitation with this approach is the lack of control over inclusion and exclusion criteria for diagnostic decisions. The ideal design is, of course, prospective and longitudinal, although this is more costly. Individuals are entered into a study and followed at specific intervals over the course of their disease only after specifically defined criteria have been documented. The criteria for diagnostic decisions are developed beforehand and similarly applied to all cases in the study. This design also permits an estimation of the reliability of diagnostic decisions.

Range of measurement Just as it is important to include appropriate comparison groups, it is also essential that individuals within one study are assessed with a broad range of clinical, laboratory and neuropathological measures. This will permit the examination of the interrelationships between scores on these measures and the determination of which measures identify differences among the dementias. As was mentioned earlier, the compartmentalization of research specialties at this stage may well hinder our progress in the understanding of the disease.

Sunnybrook Medical Centre Dementia Study

To illustrate the recommended research strategies, the following brief description of the Sunnybrook Dementia Study is provided. While this study does not incorporate all aspects, it represents a significant portion of the ideal approach to the study of Alzheimer’s disease. This study is a prospective, longitudinal investigation of 399 individuals which commenced in 1982. After careful screening and application of the recommended diagnostic criteria, the following groups were included in the study: (1) Neurologically Normal (N = 120); (2) Pure Alzheimer (N = 91); (3) Other Dementias (N = 67); (4) Mixed Alzheimer (N = 64); (5) Non-Demented (not neurologically normal) (N = 57).

Each of the 399 individuals have undergone the following clinical assessments at 12 month intervals: (a) neurological assessment of disinhibition reflexes; deep tendon reflexes; muscle tone and movements; bradykinesia; power; and extraocular movements; (b) neuropsychological assessment of the following functions: memory, intelligence, language, task, motor, auditory, psychomotor, and visuoperceptual; (c) language assessment including picture description, sentence disambiguation, and story retelling; and (d) behavioural assessment of mental disability, physical disability, socially irritating behaviour, and disengagement.

In addition, the morphometric assessments of autopsied brains include the evaluation of over 80 representative sections from frontal, temporal and parietal lobes, and including hippocampus, corpus callosum, fornix, midbrain, medulla and cerebellum.

The data generated from the extensive measurement gathered from this large sample have lent themselves to detailed multivariate analyses. To meet the research strategies recommended in this paper, a research project such as this would also benefit from involvements of other health science specialties, such as epidemiology, neuroscience and radiology. The coordination of these differing specialties would necessitate the use of the same diagnostic criteria, making it possible to corroborate the respective findings. To make this approach feasible it would also be necessary to coordinate research efforts across various Canadian centres as well as specialties, thus permitting the best utilization of resources and providing a national basis for substantial advancement of knowledge of Alzheimer’s disease.
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REFERENCES