Challenges and Opportunities of Clinicopathological Investigation in Longitudinal Studies of Alzheimer’s Disease

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ABSTRACT: After organizational involvement in a clinicopathological investigation of Alzheimer’s Disease for a decade, the present appears an appropriate time to reflect upon both the major challenges encountered as well as the exciting opportunities presented by such a longitudinal study.

Problematic areas have included: (a) brevity of research grant intervals (generally one- or two-year); (b) turnover of support personnel, as a consequence; (c) limited biostatistical and data management expertise dedicated to the Study objectives; (d) limited neuropsychological manpower in this specialized sphere; (e) “distillate” effect of postmortem retrieval, by which only some of the many clinical cases expire during any grant period, only some of those receive autopsy permission, only some of those demonstrate (pure) Alzheimer’s Disease neuropathologically, and only some are harvested quickly enough for specialized (e.g. biochemical) analyses; (f) ensuring the scientific optimization of available tissue samples; and (g) paucity of cases dying in the early stages of the illness.

Significant achievements include: (a) demonstration of the opportunities for young researchers committed to careers in behavioral neurology, psychogeriatrics or neurodegenerative pathology; (b) development of improved testing protocols for psychometric, electroencephalographic and neuroradiological evaluation of the demented elderly; (c) ethical enrolment both of a large cohort of Alzheimer patients and a sizeable normative (control) population; (d) public cooperation permitting a postmortem compliance rate exceeding 75%; (e) rapid autopsy retrieval times (50% < 6 hours); (f) utilization of human postmortem synaptosomal preparations for neurochemical investigations; (g) availability of fresh autopsy tissues for other specialized techniques (e.g. magnetic resonance spectroscopy, in situ hybridization); and (h) a collegial forum for the regular exchange of scientific data.

While the challenges to be met are certainly not unique to our Study, the interdisciplinary and longitudinal nature of this approach could magnify their potentially retardatory effect upon research quality. By contrast, however, surmounting these hurdles enables the participant scientists to share in an incomparable opportunity for observational insights into the cellular and pathogenetic mechanisms underlying the cognitive decline of Alzheimer patients. The vigour with which my numerous collaborators at the University of Western Ontario meet such challenges may serve as a model for other Alzheimer centres where a similar research system is likewise expected to justify the anticipation of its supportive funding agencies, and of the patients whom we are pledged to comfort.

RESUMÉ: Les défis et les opportunités de l’investigation clinicopathologique dans les études longitudinales de la maladie d’Alzheimer. Après avoir été impliqué pendant dix ans au niveau organisationnel dans une investigation clinicopathologique de la maladie d’Alzheimer, le moment me semble opportun de refléchir sur les défis majeurs ainsi que sur les chances excitantes qu’offre une telle étude longitudinale.

Les domaines dans lesquelles nous avons rencontré des problèmes incluent: a) la brièveté des périodes pour lesquelles des octrois sont accordés (sur une période de un ou deux ans, généralement); b) avec, comme conséquence, un roulement au niveau du personnel de soutien; c) une expertise limitée dans le domaine du traitement des données et de l’analyse biostatistique consacrés aux objectifs de l’étude; d) un personnel limité dans le domaine spécialisé de la neuropsychologie; e) un effet de “distillat” de la récupération des cas en post mortem: seulement quelques-uns des nombreux cas cliniques décèdent pendant une période donnée couverte par une subvention et on n’obtiendra la permission pour l’autopsie que pour un certain nombre de patients décédés; parmi eux, la neuropathologie sera caractéristique d’une maladie d’Alzheimer seulement dans un certain nombre de cas et seulement quelques-uns des
cerebral cortex are not t\'ô for the proper performance of special analytical (i.e., biochemical) analyses; (f) the difficulty of ensuring the availability of the most suitable equipment for the longitudinal analysis required; and (g) the rarity of these cases which are occurring in the later stages of the disease.

Given that none of the participants in the Dementia Study Group had any prior experience with a multidisciplinary, longitudinal investigation of senile dementia, it is hardly surprising that a number of problematic areas have arisen. The brief but candid review of these which follows is prompted by the ethical imperative of all researchers to learn from our (honest) mistakes and share this information for the benefit of our colleagues.

**Challenges encountered**

Given that none of the participants in the Dementia Study Group had any prior experience with a multidisciplinary, longitudinal investigation of senile dementia, it is hardly surprising that a number of problematic areas have arisen. The brief but candid review of these which follows is prompted by the ethical imperative of all researchers to learn from our (honest) mistakes and share this information for the benefit of our colleagues.

Brevity of research grant intervals causes a recurring difficulty. Most funding agencies provide financial support for only a one or two-year period, occasionally for three years. An inordinate amount of time and effort was therefore expended by our Study Group on the planning and submission of research grant application renewals. Funding organizations have naturally been reticent to support new Projects for longer intervals, particularly for a disease whose enormous incidence has only recently been acknowledged. However, improved research productivity from longitudinal investigations of this type will certainly result from project periods of at least five years, especially to established interdisciplin ary groups.

As a consequence of the brevity of many of our early grant awards, there has been an inevitable and somewhat frustrating turnover of support staff. An interval of several months is usually required to train such personnel for the laboratory, administrative, or clinical tasks involved. It is therefore extremely inefficient to lose such technicians and project assistants to more secure jobs, often just as their expertise is reaching its zenith. Of course, skilled support staff are only too aware of the recurring crises in grant renewals, and major funding bodies must reevaluate their potential for longer-term commitment to the clinicopathological approach.

Data management, using computer hardware and software, as well as bio-statistical expertise are critical components for any interdepartmental study in which relative strength of multiple correlations between numerous parameters must be weighed. Canadian funding agencies frequently assume this support will be provided by the host Faculty of Medicine. In practice, however, bio-statistical, computer programming, and data management expertise are severely limited by fiscal constraints at most Canadian universities. Superb consultative advice has been available to our Group on an informal basis, but multidisciplinary and longitudinal investigations of this nature properly require full-time support staff dedicated to the specific objectives of such a study.

In this country there are as yet few neuropsychologists with a major commitment to the development of the specialized psychometric instruments needed to study the longitudinal progression of cognitive decline in the organic dementias. As Kasznia has emphasized elsewhere in this Supplement (A.W. Kasznia, R.S. Wilson, J.H. Fox and G.T. Stebbins, this volume), psychometric measures used to compare demented patients with healthy controls which may be highly discriminating can by no means be assumed also to show the longitudinal validity required to track the expected deterioration in cognition of Alzheimer patients over many months and years. For example, psychometric instruments sufficiently sensitive to early dementia to
show very good initial discriminative validity may demonstrate
a truncation of variance ("floor effect") as the dementia severity
increases over time, and are therefore frequently not the
best choice for studies concerned with neurobiological corre­lates
of cognitive deficits in Alzheimer’s disease. This is because
such truncation in measure variance limits the magnitude of
any relationship which may be observed between a given biologi­cal (e.g., histological, biochemical) variable and the cognitive
measure under study. For these kinds of reasons, in our own
Project the earlier clinical choice of the Extended Scale for
Dementia and the London Psychogeriatric Rating Scale merits
thorough reevaluation. Such improvements will be dramati­cally facilitated as granting bodies enhance the opportunity for
neuropsychological studies of demented patients.

Particularly with an illness in which the expected life span
following medical confirmation of diagnosis averages some five
to eight years (and not infrequently approaches fifteen years),
cellular investigations dependent upon postmortem retrieval of
autopsy tissues are by definition constrained by the rate of
harvest of this CNS material. Even where the postmortem
permission rate is gratifyingly high, only some of the clinical
cases documented will expire during any grant interval; the
nearest of kin of only some of those patients will permit necropsy;
only some of those cases autopsied will show uncomplicated
or pure Alzheimer’s disease neuropathologically; and only some
postmortems can be performed soon enough after death to
permit the specialized (e.g. synaptosomal) tissue analyses
planned. Cost effectiveness is therefore exceedingly difficult to
demonstrate to reviewers of grant proposals, in the face of this
“distillate” or winnowing effect on postmortem retrieval.

In North America, there has until recently been a general
paucity of available autopsy tissue samples from well-docu­mented clinical cases of Alzheimer’s disease and the other
organic dementias. Major difficulties in sustained funding have
regrettably been encountered by national brain banks, two in
the United States and one in Canada. It is therefore crucial to
ensure the maximum scientific utilization of harvested brain
tissues from any clinopathological studies, and the special
designation by the American National Institutes of Health of
ten “centres of excellence” for Alzheimer Research should
contribute impressively to the amelioration of this problem. At
this University, we continue working to maintain an equitable
balance between the requests from local basic scientists and
those of cell biologists in several other centres. While these
precious tissue samples are provided under the auspices of
each Department of Pathology, decisions as to their ultimate
distribution are no more the sole jurisdiction of the responsible
neuropathologists than they are of the consultant clinicians or
the collaborating biochemists. A small Tissue Users’ Committee,
selected through the office of each Dean of Medicine, may be
one mechanism by which the legitimate scientific requirements
of all interested parties can be satisfactorily met.

The ease of obtaining autopsy permission, and of course the
frequency of expiration, are inversely proportional to the stage
or duration of the illness. The large majority of cases harvested
in our own Study thus far have been “end-stage” patients, who
have suffered from Alzheimer’s disease for many years. This
fact renders the histological and biochemical dissection of mean­ful pathogenetic phenomena much more difficult than in
those few instances where the patient has died in the earliest
phases of the disease. Since patients are usually not enrolled in
such a research Project until the family members have turned to
a medical practitioner for help, special efforts should be made
to enhance the interaction of such clinicopathological Projects
with community-based Memory Clinics, where large numbers
of subjects in the very earliest stages of cognitive decline may
be studied in vivo and followed sequentially, with greater chance
of incidental death from intercurrent illness providing “earlier­stage” tissue.

Exciting opportunities

Despite the challenges created by all of the above problems,
a rewarding number of significant achievements have already
been accomplished by my colleagues. It is increasingly evident
that a satisfying research career awaits those younger scientists
willing to devote their major efforts to the fields of behavioral
neurology, geriatric psychiatry, or the neuropathology of the
organic dementias. At this Medical School, many of Canada’s
pioneers in these research fields declared a collaborative intent
for Alzheimer research in spite of undiminished responsibilities
for hospital diagnostic duties, teaching and administrative tasks
and private medical practice. Some of our contributions have
been substantial, but the Deans of medical schools are ever
more aware that acceleration of such progress necessitates the
appointment of full-time investigators in these research areas.

Concomitant spin-offs for the health care system in this
country will also flow, as markedly improved testing protocols
are developed for the neuropsychological, electroencephalo­
graphic, and neuroradiological evaluation of senior citizens, to
establish more accurately the base-line values for normal aging
as well as the criteria for earlier diagnostic acumen in the
organic dementias.

The Dementia Study Group at this University has already
enrolled more than 300 demented patients and more than 150
normative control subjects, with input from the Human Ethics
Committee of the University. Efforts at educating the citizens
of southern Ontario to the nature of this longitudinal study have
provided a postmortem compliance rate which exceeds 75%,
nearly double that found at many Canadian teaching hospitals.
Favourable liaison with the regional chronic care institutions
and nursing homes has also guaranteed a very rapid autopsy
retrieval period, in which the postmortem interval 50% of the
time is less than six hours. The ready availability of fresh CNS
tissues has enabled our colleagues to pursue a variety of specia­lized investigative techniques, including preparation of synapto­somal samples for neurochemical studies; magnetic resonance
spectroscopy; and in situ hybridization. Also worthy of con­
mendation is the regularization of a (monthly) scientific mee­
ting for the collegial exchange of data and new ideas, attended
by all our collaborators and ably chaired by Professor H.
Merskey.

COMMENT

The multifaceted and longitudinal nature of a clinicopathologi­cal approach to Alzheimer’s disease can potentially magnify
the retardatory effect of several of the above problems upon the
research productivity of such a Group. It is my personal belief,
however, that the incomparable opportunity for sharing our
observational insights into the pathogenetic mechanisms in
Alzheimer’s disease will stimulate the participating scientists at
this University to surmount such hurdles with exemplary vigour.
By sharing our difficulties as openly as our achievements with colleagues in other research institutions, the Dementia Study Group at the University of Western Ontario can hopefully serve as a model for other Alzheimer centres, where a similar research configuration must ultimately justify the anticipation not only of its supporting granting agencies but also of the participating patients and their families, without whose generous involvement this work would be impossible.

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