

Brain banking in Alzheimer's disease: pitfalls and potentials

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Methodology and handling procedures

Brain banks which collect post-mortem tissue and CSF from patients who suffered from neurological disorders have become an important link between clinicians, neuroscientists and neuropathologists involved in ageing and dementia research. Due to the large variability of the material, there are many drawbacks in the use of post-mortem brains. Therefore, collecting human brain for research purposes should put emphasis on the development of a rapid autopsy system, e.g. as practised by The Netherlands Brain Bank (1) and guarantee the quality of the tissue by proper matching for the various ante and post-mortem factors and by measuring brain pH (2).

The agonal effects associated with death may influence the pH and thus a number of chemical substances in the brain. Subjects who died after a long terminal illness have a lower pH in the brain and cerebrospinal fluid (CSF) due to increased lactic acid concentrations. Lower levels of pH were found throughout the brain in cases of death following protracted illness, as compared to sudden death (3). In addition, various enzymatic activities were found to be related to pH and lactate levels in post-mortem brain in Alzheimer's disease and Down's syndrome as well as other dementias. Tissue pH has recently been reported to be a fair indicator of mRNA preservation in human post-mortem brain (4).

Measurement of brain pH provides a simple means to screen post-mortem brain and may be used as a mean to match material in case control studies of human neurodegenerative disorders.

The various enzymes, transmitter systems and other active substances in the brain have their specific cellular localization. Therefore, data obtained by biochemical assays in homogenates or tissue extracts have only a limited value and brain banks collecting specimens for research should also strive to develop techniques which leave the morphology of the tissue intact (5).

Assessment of neuropathological changes

The examination of the pathology of the various brain regions is extremely important in particular when examining a neurodegenerative disorder such as Alzheimer's disease. The neuropathological diagnosis of 'changes compatible with Alzheimer's disease' or 'no pathology' for control non-demented patients is based on the distribution and amount of plaques and tangles in sections stained by conventional histopathological staining procedures.

The research value of a brain bank depends not only on the accuracy of diagnosis of disease cases, but also on the reliability of the exclusion of disease when collecting control cases. The diagnostic procedures in a Brain Bank have two main purposes; the first is to permit the adequate storage of the samples, according to pathology. The second is to recognize diseases with an infectious potential: AIDS and Creutzfeldt-Jacob being the most often encountered.

The current criteria for the tissue diagnosis of Alzheimer's disease (AD) are not satisfactory. Estimating numbers of plaques and tangles, the degree of congophilic angiopathy, and the difficulty of adequate sampling combine to cause confusion in the minds of the pathologists and clinician.

Quantitative diagnostic criteria tend to be standardized within each bank but are applied only with difficulties to other laboratories. The reliability of neuropathological data derived from multiple centers was investigated under the auspices of Eurage. Poor concordance was observed between eleven centres with regard to plaque and tangle quantitation, and somewhat better concordance for ranking (6). The criteria most often used for the diagnosis of Alzheimer's disease are those published by Katchaturian *et al.* (7) and more recently, the CERAD protocol. Both sets of criteria are based on the estimation of the number of plaques and correlated with the clinical status and age of the patient. Plaque morphology, size and distribution are not taken in consideration, and the counting method, stain

used or section thickness are not standardized. As a result the inter-rater reproducibility is poor, particularly in cases with lower plaque densities, where diagnostic problems are most likely to occur (8).

The lack of standard neuropathological criteria for the diagnosis of AD limits the possibility to compare research protocols. Standardization of sampling protocols and agreement concerning the diagnostic criteria, possibly in a Brain Bank network, would lead to distinct advances in clinical neuro-sciences.

Biochemical markers

Monoclonal antibodies serve as an important tool in developing diagnostic markers for Alzheimer's disease and in looking for the etiology of the disease. Monoclonal antibodies can also be developed that would detect antigenic markers in tissue and CSF and may be used in the future for early diagnosis of Alzheimer's disease in living patients (9, 10). The use of biochemical tests for Alzheimer's disease in brain tissue and CSF can be used as a complement for the conventional histo-pathological techniques.

Molecular genetics

The new techniques of molecular genetics provide a promising new approach for understanding Alzheimer's disease, especially as there is a familial factor in this disease. In a small number of patients with familial AD there is a mutation in the gene which produces the amyloid precursor protein (APP). The beta amyloid protein cleaved from this protein is a major component of plaques. Apolipoprotein E (Apo-E), has been associated with plaques and tangles. The gene coding for this protein is located on chromosome 19, and the allele e4 has been found to be 3-4 times more common in sporadic cases of the disease than in controls.

Molecular genetic studies will help the scientists to locate defective genes and well characterized cell lines from clinically and post-mortem confirmed Alzheimer's disease cases. The abnormal proteins or enzymes associated with this disease can be used to produce c-DNA for linkage analysis.

By supplying clinically and neuropathologically well documented human tissue for research, brain banks for AD have become a solid bridge between the clinicians, pathologists and neuroscientists for aging and dementia research.

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