THE NETHERLANDS BRAIN BANK

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ABSTRACT

The Netherlands Brain Bank functions as a link between clinicians, neuropathologists and basic scientists by providing researchers with clinically and neuropathologically well-documented post-mortem brain samples and CSF of Alzheimer patients and controls. The unique features of this bank are the very short post-mortem delay and fresh brain dissection. In addition, the bank is involved in international standardization of the neuropathological diagnosis and the development of chemical diagnostic tests for Alzheimer's disease.

ORGANIZATION OF THE BRAIN BANK

a. Alzheimer's Disease Bank

Brain banks for neurological diseases are meant to serve as an important link between the clinician, neuropathologist and basic scientist who needs brain tissue specimens from clinically and neuropathologically well-documented patients. Considering the fact that, at present, there is no generally accepted animal model for Alzheimer's disease (AD), the availability of well-documented brain tissue of AD patients and normal controls is of crucial importance for research. In order to provide research groups with post-mortem brain tissue from AD patients and controls, a Brain Bank was established in the Netherlands Institute for Brain Research by the end of 1985, which received temporary financial support from the government, and currently structurally supported by the Royal Academy of Arts and Sciences (KNAW) and the SOOM. The organization of the Brain Bank is guided by a supervisory scientific committee, which determines its goals and evaluates the various research applications. The Brain bank provides tissue upon research protocols submitted in advance, specifying a variety of requirements, such as the age of patients and controls, total number of brains needed, agonal state post-mortem delay, exact anatomical boundaries of the brain region, kind of fixation and other treatment requirements of the tissue. This Brain Bank has two unique features: a. human brain tissue is obtained by means of rapid autopsies with a very short post-mortem delay ranging between 2-4 hours; and b. a fresh brain dissection procedure is used. The latter is a difficult regime to establish, requiring qualified staff at inconvenient times, but is a prerequisite for an increasing range of technical
Duykaerts (Paris, France). Of the 6 patients selected (women over 75 years of age), 2 were severely affected, 2 mildly affected and 2 nearly normal, as had been prospectively assessed by the Blessed test scores. Unstained paraffin embedded slides were sent to the investigators, the choice of staining techniques being left to each laboratory. A quantitative evaluation of the changes was requested in 2 specified areas of the hippocampus and in the first temporal gyrus. Subjective scores of severity and a final guess about the pre-mortem intellectual status (demented or not) were asked. Eleven forms were analyzed and a total of 14 different staining techniques was used. Absolute values of density differed much from one investigator to another, for senile plaques as well as for neurofibrillary tangles. The ranking of the slides in increasing order of severity was in good agreement for 9/11 observers concerning the neurofibrillary tangles and 3/9 observers concerning the senile plaques. The correlation between the intellectual status and the density of lesions was higher for neurofibrillary tangles than for senile plaques. The subjective scores were in better agreement for the severely affected cases than for the mildly affected ones. The lowest correlation with intellectual deficit was obtained with the quantitative scores which took into account only the senile plaques or only the hippocampal lesions. The highest correlation coefficients were obtained with the subjective scores. The observers guessed correctly the intellectual status of the 2 most affected cases and often disagreed on the intermediate and normal cases. The conclusion of this study was that the neuropathological diagnostic procedure has to be more strictly standardized before quantitative histopathological criteria can be reliably transferred from one laboratory to another, especially when mildly affected cases are involved (Duyckaerts et al., 1990).

c. Diagnostic tests

The diagnosis AD has two components: the clinical diagnosis "probable AD" and the neuropathological diagnosis. The clinical diagnosis is based on eliminating other forms of dementia. The neuropathological diagnosis is based on microscopical changes, i.e. senile plaques and neurofibrillary tangles. One also looks for the presence of dystrophic neurites as well as vascular amyloid. The alterations in AD are mainly quantitative, therefore there is always some uncertainty left in the clinico-pathological diagnosis. To come up with a possible solution for this serious problem, the Netherlands Brain Bank was requested by two American companies to evaluate recently developed diagnostic tests for AD. In the first test the concentration of Alzheimer's Disease Associated Protein (ADAP) was measured in post-mortem brain tissue samples of temporal or frontal cortex from 111 human brains using a sandwich immunoassay (Alz-EIA). ADAP has three major Alz-50 reactive subunits including A-68. This assay utilizes Alz-50 and a rabbit polyclonal antibody raised against a highly ADAP-enriched brain protein fraction in a sandwich enzyme immunoassay format. The frequently observed cross-reactivity of Alz-50 with normal
brain components in direct immunoassays is minimized by this configuration. There were 27 normal controls (NC), 28 neurological disease controls (NDC), and 53 AD patients, and 3 older Down syndrome patients with Alzheimer’s neuropathology D/AD. NC and NDC cases had essentially no detectable level of ADAP. ADAP was clearly detected in 93% of the 43 AD cases and 100% of D/AD cases (Ghanbari et al., 1990). Clinical dementia, senile plaques, and old age perse were not correlated with increased ADAP levels. The classical diagnosis of AD by the neuropathologist requires experience and is very time consuming. As the use of the tissue kit is quick and simple as well as quantitative and reliable, it can be helpful for the neuropathologists to quantify the AD changes in the brain (Ravid et al., 1990). The second test is meant for diagnosis of AD in the CSF during life and makes use of the monoclonal antibody 5-25. We are currently evaluating the test by assaying CSF samples obtained by lumbar punctures of probable AD patients, patients suffering from non-Alzheimer dementia and controls subjects as well as post-mortem CSF samples from AD patients and controls obtained by rapid autopsies. This will enable us to test the specificity, sensitivity and predictive value of CSF reactivity.

d. Future lines

As appears from applications of many research groups, similar Brain bank facilities are needed for research on neurological and psychiatric diseases other than AD, such as Parkinson’s Disease, Multiple Sclerosis (Ravid and Swaab, 1989), Depression, Schizophrenia, Huntingtons’s Disease, Multi Infarct Dementia, Binswanger Disease, Creutzfeldt-Jacob Disease, Korsakoff, developmental disturbances, endocrine syndromes, while, in addition, plasma and CSF collections are required. A start has already been made by Prof. J.M.B.V. de Jong and Dr. D. Troost with the establishment of an Amyotrophic-Lateral-Sclerosis Bank, which, at present, has at its disposal post-mortem tissue from 66 patients with an average post-mortem delay of 14 hours. The infrastructure needed for collecting brain tissue of Parkinson patients and MS patients is investigated and preliminary contacts have been established between the Brain Bank and several national and international research groups. In addition, there have been some preliminary contacts with psychiatric hospitals and research groups working on depression and schizophrenia.

By supplying clinically and neuropathologically well documented brain tissue for research the Netherlands Brain Bank hopes to form the necessary link between basic research and medical research in their effort to investigate causes, mechanisms, diagnosis and possible therapies for devastating diseases.
REFERENCES


