Application of research criteria for dementia in common clinical practice

abnormalities. Their neuropsychological profile approached that of a fronto-subcortical pattern. Episodic irritability, violence and aggression, schizophreniform psychotic episodes and periods of catatonic behavior were frequent. In distinction with Alzheimer's, none of the NCC demented patients got lost in familiar surroundings, when in clear consciousness. Delirium was common.

The results suggest that Alzheimer's and NCC dementias present different clinical courses.

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PREDICTORS OF INSTITUTIONALIZATION AMONG PATIENTS WITH ALZHEIMER'S DISEASE AND OTHER DEMENTIAS. *Mona Baumgarten, Rubin Becker (St. Justine Community Health Department and McGill University, Montreal, Canada).

The social, psychological, and economic costs associated with institutionalization of the dependent elderly are high. Therefore, a major management goal in the care of patients with Alzheimer's disease or another dementia is to maintain the patient in the community for as long as possible. As part of a study on the health of family caregivers (CGs) of patients with dementia, our objective was to identify characteristics of patients and CGs which were predictive of institutionalization over a one year interval. Patients (n=85) with a DSM-III diagnosis of dementia were recruited from the geriatric assessment unit of a large Montreal teaching hospital. All patients were residing in the community when the study began. Those who were referred to the geriatric unit specifically for pre-placement assessment or for a serious, acute medical problem were excluded. Data were obtained through home interviews with the family CG and from the geriatric unit's medical charts. At one-year follow-up, 8% of the patients had died and 34% had been institutionalized; patients who had died were not included in subsequent analyses. When contrasted with patients who were still living in the community, patients who had been institutionalized were significantly older and more cognitively impaired, and had a higher level of dependence with respect to activities of daily living. They were also more likely to be male and had a longer mean duration of dementia, although these variables were not statistically significant. Patients whose CG was a child rather than the spouse had a higher probability of institutionalization. A higher baseline level of depression among CGs was predictive of institutionalization, although the CG's physical health status (as measured by the number of reported chronic conditions) was not. Although most of the factors predictive of institutionalization are not preventable, knowledge of these factors can help clinicians and community health practitioners to target patients and families who are at high risk, and to implement appropriate preventive and therapeutic strategies.

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FAMILIAL ALZHEIMER'S DISEASE: STUDY OF A NEW ITALIAN KINDRED. L. Bergamini, * I. Rainero, L. Pinessi, G. Vaula; Dept. of Neurology, Univ. of Turin (Italy); A.C. Bruni, G. Gei, M.P. Montesi, C. Ermio; Dept. of Neurology, Lamezia Terme (Italy); and J.F. Foncin; Hop. La Salpétrière, Paris (France).

We have recently discovered in Torino (Italy) a new pedigree with Familial Alzheimer's disease. The index patient is a woman who became demented at age 43. Several relatives have had a history of dementia. The ancestors of the patient were from Calabria (Southern Italy) and members of the family emigrated to the North of Italy, to France and to the USA.

At present, the "Torino family" comprises 1085 members, distributed in 8 generations.24 members affected with Alzheimer's disease have been identified: 5 were diagnosed by personal examination, 12 by medical records and 7 by history. Mean age at death of the patients is 50.5 ± 9.2 yr (range 43-59). The pedigree is consistent with autosomal dominant inheritance.

The "Torino family" shows several similarities with the Family N, described by Foncin et al. (1): the ancestors were born in the same country of Calabria, neurological and psychiatric symptoms are the same in the two families and no difference in age at onset of the disease and age at death was found. We are trying to find a direct linkage between these two kindreds.

Molecular genetic of this new family is currently under investigation.

1.Foncin JF et al. Rev.Neurol (Paris), 141:194-202,1985.

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DIFFERENCES IN POSTURAL SWAY PATTERNS IN INDIVIDUALS WITH ALZHEIMER DISEASE WITH AND WITHOUT HISTORY OF FALLS: A Pilot Study. A. Bhattacharya and C. Cox, Dept. of Environmental Health; S. Gilster, Alois Alzheimer Center; A. McCracken, College of Nursing; and G. Warshaw, Geriatric Division of the University of Cincinnati Medical School; Cincinnati, Ohio, U.S.A.

Persons with Alzheimer's Disease (AD) have more than three times the risk of falling than cognitively healthy elderly persons. Regardless of the physiological conditions for which falling is a marker, the most significant risk factor is the impairment of postural balance. In an effort to determine the ability to perform quantitative postural sway measurements in the subjects with AD and differences in postural sway patterns in patients with and without history of falls, a pilot study with 2 male and 2 female patients was performed. Out of 4 patients (mean age: 84.7 yrs.), 2 had previous history of falls. Postural sway testing was conducted on these patients with Haycox Rating Scale scores of 16 to 26. The postural balance or sway was noninvasively quantitated with a microprocessor-based force platform system. Each patient performed four tasks i.e., EO: Eyes open on force plate; EC: Eyes closed on force plate; FO: Eyes open on foam pad placed on the force plate; and FC: Eyes closed on foam pad placed on the force plate. This test allows quantification of the movement pattern of body's center of pressure associated with postural sway. These tests were designed to indirectly evaluate the roles of vision, proprioception and the vestibular system for postural balance. The patients with previous history of falls had difficulty in completing FO and FC tests. In particular, postural sway responses for the fallers were significantly larger than the nonfallers for the FO(up to 3.9 times) and FC(up to 4.7 times) tests where the vestibular system is placed at a higher challenge compared to EO and EC tests. Furthermore, frequency of sway patterns in the fallers (0.08 Hz for lateral sway and 0.11 Hz for anterior-posterior[A-P] sway) were low compared to the nonfallers(0.18 Hz for lateral sway and 0.23 Hz for A-P sway) which is consistent with vestibular-controlled postural balance characteristics. In summary, the result of our above-mentioned case study indicates that postural sway testing can be safely performed in the Alzheimer patients and there exists a significant difference in postural sway response between fallers and nonfallers.

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APPLICATION OF RESEARCH CRITERIA FOR DEMENTIA IN COMMON CLINICAL PRACTICE *F.R.J. Verhey, R.W.H.M. Ponds, E.J. Reyerson van Buuren, F.W. Vreeling and J. Jolles, Departments of Neuropsychology and Psychobiology and *Neurology; University of Limburg, P.O. Box 616, 6200 MD Maastricht, The Netherlands

Recently, diagnostic criteria were proposed for the clinical and research diagnosis of dementia and Alzheimer's Disease (AD) with the aim of reaching a higher degree of homogeneity in patient-groups (DSM-III-R and NINCDS/ADRDA). The present study addresses the question whether, and to what extent, a diagnostic approach based upon the recommended procedures leads to an outcome which is different from the diagnoses based upon the approach in routine specialist practice. 234 consecutive admissions to a specialized Alzheimer Center (the Maastricht Memory Clinic MMC) were compared to diagnoses made previously by referrers who had not used such a model. All patients (mean age 62.8 years) were referred because of a memory problem, which could vary from mild subjective complaints to severe dementia. All patients underwent a standardized diagnostic procedure, which included a semi-structured interview with the patient and his informant, an extended neuropsychological testbattery, bloodtests, and CT-scan. Furthermore, the following scales were used: the Global Deterioration Scale, the Blessed Dementia Scale, the Hamilton Rating Scale for Depression, the Mini-Mental State Examination and Hachinski Ischemic Score. Prior to evaluation in the MMC, the original diagnosis of the referrer was obtained from an admission form. The results were as follows: the diagnosis was changed in 66 out of 166 patients. Out of 73 patients, referred as a dementia, the diagnosis was changed in 32 cases (44%): in 12 cases, the criteria for dementia were not met: in 6 cases the deficit was focal and in 6 other cases the deficits were not severe enough to interfere with social activities. The etiologic diagnosis changed in 14 cases. AD was overdiagnosed in 12 cases. In 6 of these, history taking revealed cerebrovascular factors, previously unknown. On the other hand, the diagnosis of dementia was made in 34 (21%) of 161 patients, previously not diagnosed as such. These were all cases of mild dementia. This study shows that the extensive approach as recommended for research leads to substantial

changes in diagnostic outcome, compared to procedures in daily practice. Most of the discrepancies pertain to the evaluation of the clinical condition. This underlines the importance of a thorough, albeit time consuming, clinical evaluation, which cannot be replaced by laboratory and X-ray data. The diagnosis of dementia and dementing diseases should be based on an integrated multi-disciplinary and systematic model, with explicit definitions of terms and taking into account all in- and exclusion criteria.

BRAIN AMYLOIDOSIS

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PATHOGENESIS OF BETA-AMYLOID FIBER FORMATION.

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Amyloid deposition in the brain accompanies normal aging and AD as well as unconventional viral disease and Down's syndrome. In each case, the amyloid deposits exhibit generally similar morphologies but with differences characteristic for each condition. In all of the above mentioned conditions, the presence of amyloid fiber deposits appears to be limited to the CNS. However, by means of in situ hybridization and immunohistochemical methods, it has been shown that many cell types within and outside the CNS could be the source of the beta-protein in Alzheimer disease (AD). Ultrastructural studies strongly indicate that the resident macrophage population of cells in the brain, the microglia, are the cells producing the beta-amyloid fibers. These cells, which contain a labyrinth of amyloid-filled channels, show a clear polarity in relation to the amyloid deposits. The amyloid fibers appear to form in altered cisterns of endoplasmic reticulum, and there is some indication that the beta-protein may bypass the Golgi complex. Because the amyloid fibers are first seen in the distended cisterns of the smooth endoplasmic reticulum system, it appears that these cells are engaged in the formation, not the phagocytosis, of the amyloid fibers. The configuration of extracellular bundles of amyloid fibrils radiating from indentations in the cytoplasm of Kupffer and reticular cells of the liver and spleen in systemic amyloidosis has been found to be identical in many details with amyloid star formation by microglial cells in AD brain. We hypothesize that the microglia/ macrophages (which are probably both the producer and processor cells) synthesize and secrete the beta-peptide either as an overexpressed, truncated gene product or as an aberrant peptide resulting from abnormal post-translational processing.

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AMYLOID βA4 PROTEIN PATHOLOGY IS CENTRAL TO THE CAUSE OF ALZHEIMER'S DISEASE

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On the molecular level Alzheimer's disease (AD) is characterized by amyloid βA4 protein, which accumulates primarily in the hippocampus and neocortex. The massive deposition of fibrillar βA4 protein aggregates found in AD brain is reminiscent of storage diseases. The preclinical period of amyloid βA4 protein accumulation was estimated by us to approximate 30 years.

Since the same molecular neuropathological changes are observed in trisomy 21 Down's syndrome, the AD amyloid βA4 pathology is suggested to be due to abnormal expression of genes located on human chromosome 21.

The demonstration of the gene (PAD/APP) encoding the amyloid precursor protein (Pre A4) to map to chromosome 21 strongly supports our hypothesis that this gene and its pathological product is central to the causation of AD.

The exon structure of the PAD gene revealed that amyloid βA4 protein can not be produced by alternative splicing and therefore has to be generated by abnormal pathological degradation of transmembrane Pre A4 proteins which in contrast to secretory Pre A4 proteins include the βA4 sequence as part of the ecto- and transmembrane domains.

Since the amyloidogenic transmembrane Pre A4 proteins are abundantly expressed in neurons, anteriogradely transported in axons and located at synapses, the pathological degradation to βA4 protein has to occur either in neurons or between synapses.

Thus, chronic extra- and intracellular amyloid βA4 protein formation in brain would occur at sites relevant for impairment of intellectual functions, gradually reduce the synaptic density and finally result in the clinical features of AD.

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AMYLOID β-PROTEIN DEPOSITION AS A SEMINAL PATHOGENETIC EVENT IN AD: AN HYPOTHESIS. *D.J. Selkoe. Harvard Medical School and Brigham and Women's Hospital, Boston, MA 02115.

Evidence emerging from numerous laboratories during the last two years suggests that amorphous, largely non-fibrillar deposits of the amyloid β-protein (AβP) precede the development of neuritic plaques, neurofibrillary tangles, gliosis and other cytological changes in Alzheimer's disease (AD) and Down's syndrome (DS). We studied such diffuse plaques to advantage in AD cerebellum and striatum, where they are virtually the only form of AβP deposit found even at the end of the disease (Joachim et al., Am. J. Path. 135:309, 1989 and J. Neuropath. Exp. Neurol. 87:330, 1989). If local neuronal/neuritic alteration were a prerequisite for AβP deposition, one would expect some morphological evidence of neuritic abnormality after years of cerebellar and striatal AβP deposition, particularly since profound neuritic pathology surrounds many AβP deposits in cerebral cortex. Similarly, sizable numbers of diffuse AβP deposits can be found in some 25-35 year old DS subjects at a time when no neuritic or glial abnormality is detectable. Recently, we discovered AβP-immunoreactive deposits in vessels and/or perivascular tissue of skin and other non-neural tissues in AD and DS, suggesting that AβP deposition can occur in the absence of neuronal or glial injury, indeed, in the absence of neurons and glia. These and other observations all strongly suggest that β-amyloidosis in AD, like other better characterized amylodioses, is not secondary to local cellular change but precedes it. We, therefore, hypothesize that in normal aging, an alternate, minor pathway for APP proteolytic processing exists that results in release of amyloidogenic fragments of APP containing the intact AβP region. In DS, this alternate pathway, which is normally used at a low level, is overutilized due to the increased expression of APP molecules that results from higher gene dosage. In FAD, rearrangements or mutations on ch. 21 (in at least some families) lead to a dysregulation of APP biosynthesis that results in more APP molecules being processed through the minor pathway and increased genesis of AβP, producing a histologic phenotype that is indistinguishable from that of DS. The progressive deposition of AβP in DS and FAD initiates, either directly or indirectly, a cascade of secondary cellular changes (including local neurite growth) that, over years or decades, produce neuronal dysfunction and thus dementia.

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ROLE OF IMMUNE FACTORS IN AMYLOIDOGENESIS IN ALZHEIMER BRAIN T. Ishii, S. Haga, M. Satoh, and F. Kametani, Psychiatric Research Institute of Tokyo, Setagaya-Ku, Tokyo 156, Japan.

The earliest stage of deposition of amyloid protein and fibril formation (amyloidogenesis) in the Alzheimer brain was studied by immunohistochemical methods using antibodies to subsequences of amyloid precursor protein (APP), immunoglobulins (IG), complements (CP), α1-antichymotrypsin (ACT) and microglia.

IG, CP C1q, C4, C3 and ACT are present in "diffuse plaques" which are thought to be the earliest stage of amyloid deposition. In addition, the monoclonal antibody to senile plaques which was reported previously (Ishii et al., Neuropathol & Appl Neurobiol 12, 1986) proved to react with epitopes in the light chain of IGs, thus indicating the presence of the latter epitopes in close association with the amyloid fibrils in the Alzheimer brain. In the case of complement immunohistochemistry, immuno-EM pictures revealed the deposition of a homogeneous material (probably preamyloid substance) near the immunoreactive amyloid fibrils, indicating the possible role of CP fixation in fibril formation. Microglial cells are few in number in the area of diffuse plaques but later the numbers increase and microglia accumulate in and around mature plaques. The above immunological factors are thought to be secreted by activation of macrophages through interleukin 1 and the process may be interpreted as a kind of chronic inflammation. The problem is what kind of antigen or antigens stimulate such an immunological response in the process of amyloid deposition in the Alzheimer brain.

Aberrant catabolism of APP with membrane damage is proposed as the cause of amyloid formation. Certainly trophic as well as toxic effects of β-protein are reported. However, abnormal breakdown products of physiological substances usually lead to