abnormalities. Their neuropsychological profile approached that of a fronto-subcortical pattern. Episodic irritability, violence and aggression, schizophrenia-like 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 clear consciousness was follow. 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 Baumgartner, Rubin Becker (St. Justine Community Health Department and McGill University, Montreal, Canada).

The social, psychological, and economic costs associated with institutionalisation 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 (COs) of patients with dementia, our objective was to identify characteristics of patients and COs which were predictive of institutionalisation 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 preparation of institutionalisation for, or threat of, serious, acute medical problems were excluded. Data were obtained through home interviews with the family CO and from the geriatric unit's medical charts. At one-year follow-up, 8% of the patients had died and 34% had been institutionalised: 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 institutionalised in particular, post mortem were less often male and had a longer mean duration of dementia, although these variables were not statistically significant. Patients whose CO was a woman rather than the spouse had a higher probability of institutionalisation. A higher baseline level of depression among COs was predictive of institutionalisation, although the CO's physical health status (as measured by the number of reported chronic conditions) was not. Although most of the factors predictive of institutionalisation are not statistically significant, 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); J.F. Foncin; I.R. Kindred. L. Bergamini, *I. Rainero, L. Pinessi, G. Vaula; Dept. of Neurology, Univ. of Turin (Italy); J.F. Foncin; I.R. Kindred. I.R. Kindred.

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.


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DIFFERENCES IN POSTURAL SWAY PATTERNS IN INDIVIDUALS WITH ALZHEIMER'S DISEASE WITH AND WITHOUT HISTORY OF FALLS. A Pilot Study. A. Bhattacharya and C. Cox, Dept. of Environmental Health; S. Gillster, 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 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: 85.7 yrs.), 2 had previous history of falls. Postural sway testing was conducted on these patients with Haycock's Scale scores of 6 to 26. The posterior 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 characteristics 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 EG 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 tests 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. Vethey, R.W.H.M. Ponds, E.J. Re Yetson van BtJumm, F.W. Vreeling and J. Joles, Departments of Neuropsychology and Psychobiology and *Neurology; University of Limburg, P.O. Box 816, 5000 MD Maastricht, The Netherlands.

Recently, diagnostic criteria were proposed for the clinical and research diagnosis of dementias and Alzheimer's Disease (AD) with the aim of reaching a higher level of homogeneity in patient groups (DSM-III-R and NINCDCSADRD). 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 on the clinical approach. 234 consecutive admissions to a specialized Alzheimer Center (the Maastricht Memory Clinic MMC) were compared to diagnoses made previously by referring physicians who had not used such a model. All patients (mean age 82.9 years) were referred because of a memory problem, which could vary from mild subjective complaints to severe dementia. All patients participated in a semi-structured interview with the patient and his informant, an extended neuropsychological test battery, blood tests, and CT-scan. Furthermore, the following scales were used: the Global Deterioration Scale (Reisberg), the Blessed Deterioration Scale (Reisberg), the Hamilton Rating Scale for Depression, the Mini-Mental State Examination and Hickinlton Ia tic Sore. Prior to evaluation in the MMC, the original diagnosis of dementia was obtained from a neurologist who interviewed the patient. The disease was changed in 65 out of 185 patients. Out of 73 patients, referred as a dementia, the diagnosis was changed in 52 cases (44%): in 12 cases the deficit was focal and in 8 other cases the deficits were not severe enough to interfere with social activities. The etiological diagnosis changed in 14 cases. AD was overdiagnosed in 12 cases. In 6 of these, history taking revealed cerebrovascular factors. Previously undiagnosed AD was missed in 16 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
BRAIN AMYLOIDOSIS

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 microglial/macrophage cells are engaged in a secondary processing event resulting in an aberrant production of amyloid that can occur in the absence of neuronal or glial injury, indeed, in the absence of neurons and glia. These and other observations strongly suggest that the amyloidosis in AD, like other better characterized amyloidoses, is not secondary to local cellular change but precedes it. We, therefore, hypothesize that the beta-protein is produced in normal aging, an alternate minor pathway for APP proteolytic processing exists in the brain and results in the production of APP containing the intact Aβ 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 genetic dosage. In FAD, resistance to the degradation of APP, in at least some families) lead to a dysregulation of APP biosynthesis that results in the production of APP molecules being processed through the minor pathway and increased genesis of Aβ, producing a histologic phenotype that is indistinguishable from that of DS. The progressive deposition of Aβ 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.

AMYLOID B-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 β-protein (Aβ) protein, which accumulates primarily in the hippocampus and neocortex. The massive deposition of fibrillary Aβ protein aggregates found in AD brain is reminiscent of storage diseases. The preclinical period of amyloid β-protein accumulation was estimated by us to approximate 30 years. Since the same molecular neuropathological changes are observed in Down’s syndrome (DS) in the AD amyloid β-protein pathology is suggested to be due to abnormal post-translational processing of the APP gene product. 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 β-protein can not be produced by alternative splicing and therefore has to be generated by abnormal pathological degradation of transmembrane Pre A4 protein which in contrast to secretory Pre A4 proteins include the Aβ4 sequence as part of the ecto- and transmembrane domains.

Since the amyloidogenic transmembrane Pre A4 proteins are abundantly expressed in neurons, are transported in axons and located at synapses, the pathological degradation to Aβ4 protein has to occur either in neurons or between synapses. Thus, chronic extra- and intracellular amyloid Aβ4 protein formation in brain would occur at sites relevant for impairment of intellectual functions, gradually reducing the synaptic density and finally result in the clinical features of AD.

AMYLOID β-PROTEIN DEPOSITION AS A SEMINAL PATHOGENETIC EVENT IN AD: AN HYPOTHESIS.

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Evidence emerging from numerous laboratories during the last two years suggests that amyloid β-protein (Aβ) precedes 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 Aβ deposit found even at the end of the disease (Johinik et al., Am. J. Path. 135:309, 1985 and J. Neuropath. Exp. Neurol. 87:330, 1989). If local neuronal/neuritic alteration were a prerequisite for Aβ deposition, one would expect some morphological evidence of neuritic abnormality many years before of cerebellar and striatal Aβ deposition, particularly since profound neuritic pathology surrounds many Aβ deposits in cerebral cortex. Similarly, sizable numbers of diffuse Aβ 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 Aβ-immunoreactive deposits in vessels and/or perivascular tissue of skin and other non-neural tissues in AD and DS, suggesting that Aβ deposition can occur in the absence of neuronal or glial injury, indeed, in the absence of neurons and glia. These and other observations strongly suggest that β-amyloidosis in AD, like other better characterized amyloidoses, 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 in the brain and results in the production of APP containing the intact Aβ 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 genetic dosage. In FAD, resistance to the degradation of APP, in at least some families) lead to a dysregulation of APP biosynthesis that results in the production of APP molecules being processed through the minor pathway and increased genesis of Aβ, producing a histologic phenotype that is indistinguishable from that of DS. The progressive deposition of Aβ 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.

ROLE OF IMMUNE FACTORS IN AMYLOIDOPATHY IN ALZHEIMER BRAIN

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The earliest stage of accumulation of extracellular β-amyloid fibril formation (amyloidogenesis) in the Alzheimer brain was studied by immunohistochemical methods using antibodies to subsequences of amyloid precursor protein (APP), immunoglobulins (Ig), complement (C3), α1-antichymotrypsin (ACT) and microglia. Ig, C3, 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 IgGs and thus indicate the presence of the latter epitopes in close association with the amyloid fibrils in the Alzheimer brain. In the case of complement immunohistochemistry, immuo-EM pictures revealed the deposition of a homogenous material (probably amyloid 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 microglial accumulate in and around mature plaques. The above immunological factors are thought to be secreted by 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. Apart from catalysis of amyloidogenesis it is proposed as the cause of amyloid formation. Certainly trophic as well as toxic effects of-beta-proteins are reported. However, abnormal breakdown products of physiological substances usually lead to...