Application of research criteria for dementia in common clinical practice

Citation for published version (APA):

Document status and date:
Published: 01/01/1990

Document Version:
Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license above, please follow below link for the End User Agreement:
www.umlib.nl/taverne-license

Take down policy
If you believe that this document breaches copyright please contact us at: repository@maastrichtuniversity.nl
providing details and we will investigate your claim.

Download date: 14 Sep. 2023
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 NCE demented patients get lost in familiar surroundings, when in clear consciousness. 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.


188 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. 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 tests in the subjects with AD and differences in postural sway patterns in patients with and without history of falls, a pilot study was performed. 2 male and 2 female patients was performed. Out of 4 patients (mean age: 86.7 yrs.), 2 had previous history of falls. Postural sway testing was conducted on these patients with Haycock Balance Scale scores of 6 to 26. The postural 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; 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 tests conducted for fallers can be safely employed in the Alzheimer patients and there exists a significant difference in postural sway response between fallers and nonfallers.

189 APPLICATION OF RESEARCH CRITERIA FOR DEMENTIA IN COMMON CLINICAL PRACTICE. *F.R.J. Vanheuvelen, F.A.M. Ponds, E.J. Reveson van Baaren, F.W. Vreeling and J. Joles, Departments of Neuropsychology and Psychopathology 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 research groups (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 on a more generalized approach. 234 consecutive admissions to a specialized Alzheimer Center (the Maastricht Memory Clinic MMC) were compared to diagnoses made previously by raters who had not used such a model. All patients (mean age 62.9 years) were referred because of a memory problem, which could vary from mild subjective complaints to severe dementia. All patients underwent a diagnostic battery 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 Depression 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 dementia was obtained from a neurologist, psychiatrist or other professional. Of 234 patients, the diagnosis was changed in 65 out of 186 patients. 67 of 73 patients, referred as a dementia, the diagnosis was changed in 32 cases (44%): In 12 cases the diagnosis was unchanged, in 6 cases the deficit was focal and in 6 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 onset of regular fallers previously undiagnosed. 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 underscores 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**

190

**PATHOGENESIS OF BETA-AMYLOID FIBER FORMATION.**


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 lattice 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.

191

**AMYLOID B4 PROTEIN PATHOLOGY IS CENTRAL TO THE CAUSE OF ALZHEIMER'S DISEASE.**


#Department of Pathology, University of Melbourne, Parkville, Victoria 3052 Australia

On the molecular level Alzheimer's disease (AD) is characterized by amyloid B4 protein, which accumulates primarily in the hippocampus and neocortex. The massive deposition of fibrillar B4 protein aggregates found in AD brain is reminiscent of storage diseases. The precursory period of amyloid B4 protein accumulation was estimated by us to approximate 30 years. Since the same molecular pathological changes are observed in trisomy 21 Down's syndrome, the AD amyloid B4 pathogenesis 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 (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 B4 protein can accumulate in and around mature plaques. The above pathological degradation of B4 protein has to occur either in neurons or between synapses. Thus, chronic extra- and intracellular amyloid B4 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.

192

**AMYLOID B-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 amyloid, largely non-fibrillar deposits of the amyloid B-protein (ABP) 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 ABP 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 ABP deposition, one would expect some morphological evidence of neuritic abnormality after years of cerebellar and striatal ABP deposition, particularly in some young AD subjects at a time when no neuritic or glial abnormality is detectable. Recently, we discovered ABP-immunoreactive deposits in vessels and/or perivascular tissue of skin and other non-neural tissues in AD and DS, suggesting that ABP 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 B-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. The results of recent immunohistochemical studies show that amyloidogenic fragments of APP containing the intact ABP region. In DS, this alternate pathway, which is normally used at a low level, is upregulated due to the increased expression of APP molecules that results from higher genetic dosage. In AD, a minor proportion of APP is synthesized as a secreted fragment containing the intact ABP region. This upregulated pathway, which occurs in AD, may be due to a cascade of secondary cellular events. The progressive deposition of ABP 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.

193

**ROLE OF IMMUNE FACTORS IN AMYLOIDOSIS.**

*T. Ishii, S. Haga, M. Satoh, and F. Kametani, Psychiatric Research Institute of Tokyo, Setagaya-Ku, Tokyo 156, Japan*

The earliest stage of amyloid fibril formation (amyloidogenesis) in the Alzheimer brain was studied by immunochemical methods using antibodies to subsequences of amyloid precursor protein (APP), immunoglobulins (Ig), complement (C), α-1-antichymotrypsin (ACT) and microglia. Ig, 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 13:309, 1989 and J. Neuropath. Exp. Neurol. 87:330, 1989). If local neuronal/neuritic alteration were a prerequisite for ABP deposition, one would expect some morphological evidence of neuritic abnormality after years of cerebellar and striatal ABP deposition, particularly since profound neuritic pathology surrounds many ABP deposits in cerebral cortex. Similarly, sizable numbers of diffuse ABP 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 ABP-immunoreactive deposits in vessels and/or perivascular tissue of skin and other non-neural tissues in AD and DS, suggesting that ABP 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 B-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. The results of recent immunohistochemical studies show that amyloidogenic fragments of APP containing the intact ABP region. In DS, this alternate pathway, which is normally used at a low level, is upregulated due to the increased expression of APP molecules that results from higher genetic dosage. In AD, a minor proportion of APP is synthesized as a secreted fragment containing the intact ABP region. This upregulated pathway, which occurs in AD, may be due to 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 AMYLOIDOSIS IN ALZHEIMER BRAIN.**


On the molecular level Alzheimer's disease (AD) is characterized by amyloid B4 protein, which accumulates primarily in the hippocampus and neocortex. The massive deposition of fibrillar B4 protein aggregates found in AD brain is reminiscent of storage diseases. The precursory period of amyloid B4 protein accumulation was estimated by us to approximate 30 years. Since the same molecular pathological changes are observed in trisomy 21 Down's syndrome, the AD amyloid B4 pathogenesis 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 (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 B4 protein cannot 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 B4A sequence as part of the ecto- and transmembrane domains.

Since the amyloidogenic transmembrane Pre A4 proteins are abundantly expressed in neurons, anteriorly transported in axons and located at synaptic vesicles, the pathological degradation of B4A protein has to occur either in neurons or between synapses. Thus, chronic extra- and intracellular amyloid B4 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.