NEUROLEPTIC MEDICATION WORSENS THE COGNITIVE DECLINE OF DEMENTIA

R. McShane, T. Hope, R. Jacoby. *Section of Old Age Psychiatry, Warneford Hospital, Oxford, OX3 7JX, UK*

Background: Patients with dementia who also have the non-cognitive symptoms of aggression, psychosis or sleep disturbance have a faster rate of subsequent cognitive decline than those without. The possibility that neuroleptic medication, which is often used to treat these symptoms, accounts for this phenomenon has not previously been examined.

Method: As part of a longitudinal study of behaviour in dementia, the cognitive function of 71 subjects with dementia was assessed every four months on at least six occasions using an expanded version of the MiniMental State Examination (MMSE) and non-cognitive symptoms were rated using the Present Behavioural Examination. Linear regression was used to establish which of the following independently contributed to more rapid decline: neuroleptic use, physical aggression, sleep disturbance, persecutory ideas, hallucinations, sex, age, duration of illness and initial level of cognitive function. Neuropathology was available in 37 cases.

Results: Those who took neuroleptics declined twice as fast as those who did not (MMSE decline over 20 months: 10.3 ± 1.5 versus 5.1 ± 0.7, $p = 0.006$). Although cognitive decline was also greater amongst those with more severe persecutory ideas, aggression and sleep disturbance, only the use of neuroleptics and the severity of persecutory ideas *independently* contributed to more rapid cognitive decline. Furthermore, in 20 subjects who started neuroleptics after study entry, the rate of decline was significantly greater over the year after the start of the medication than in the previous year. Cortical Lewy body pathology did not affect these results.

Conclusion: The neuroleptic medication used to treat behavioural problems in dementia worsens the already poor cognitive function.

APOLIPOPROTEIN E POLYMORPHISM, CALCIUM AND ALZHEIMER'S DISEASE

Wolfgang Müller [1], Karin Berlin [1], Winfried März [2], Thomas G. Ohm [3]. [1] *Institute of Physiology, Charité, Charité, 10098, Berlin;* [2] *Dept. of Clinical Chemistry, University Freiburg;* [3] *Institute of Anatomy, Charité, 10098, Berlin, FRG*

Both, A4-β-amyloid and apolipoprotein E (apoE) have been implicated as major factors in the pathophysiology of Alzheimer's disease. The in vitro observed neurotoxicity of β-sheeted βA4-amyloid appears to be in part mediated by a disturbance of Ca-homeostasis. The pathogenic mechanisms however of apoE is still obscure. In vitro, apoE isoforms bind to βA4 amyloid. Moreover, Alzheimer's disease related antigens are induced by increased intracellular Ca-levels. The present study analyses the effects of βA4 amyloid, apoE and their complexes on intracellular calcium concentrations as measured by FURA-2/AM image analysis. Hippocampal neurons of E18 rat pups were cultivated for between three and five weeks before measuring the intracellular calcium level. Synthetic βA4 amyloid (1–43 mer; Bachem; 20 μMol), and recombinant apoE3 isoforms (PanVERA) were used. These compounds were incubated, either alone or together, overnight at 37°C. The respective compound was added to the cells bath solution and, after being incubated for four minutes, removed by washing for a 16 minute period. After this, the next compound was applied to the same cells. In order to avoid bias due to the order of application, the application sequence was varied. Synaptic network and consecutive bursting due to rebound excitation was blocked by 10 μMol CNQX. A significant co-operative effect was observed for βA4/apoE complexes (Table 1)

	ΔCa	$\overline{\Delta Ca}$
βA4	92%	
ApoE3	120%	
βA4/E3	204%	270 nM

resting $\overline{Ca} \sim 100$ nM; 3 cultures/total n $\approx$ 100 neurons

We conclude that apoE plays an important role in conjunction with A4-β-amyloid in the disturbance of Ca-homeostasis, neurotoxicity and induction of Alzheimer's disease related antigenetic changes.

DIFFERENTIAL DIAGNOSIS OF DEPRESSION AND DEMENTIA IN GERIATRIC PATIENTS BY QUANTITATIVE MAGNETIC RESONANCE IMAGING

J. Pantel [1], H. Dech [1], M. Essig [2], M.V. Knopp [2], L.R. Schad [2], M. Friedlinger [2], D. Popp [1], J. Schröder [1]. [1] *Department of Psychiatry, University of Heidelberg, Vossstrasse 4, 69115 Heidelberg;* [2] *German Cancer Research Institute (DKFZ), Im Neuenheimer Feld 280, 69120 Heidelberg, Germany*

The differentiation between depression and dementia in elderly patients can be complicated by the fact that some degree of cognitive dysfunction or "pseudodementia" is frequently observed in depression. In order to improve differential diagnosis, we used quantitative magnetic resonance imaging (MRI) to investigate volumes of different brain structures in patients and controls. Up to now, 13 patients fulfilling the criteria of major depression (DEP, DSM-III-R: 296.), 21 age and sex matched patients with dementia of the Alzheimer type (DAT/ NINCDS/ADRDA criteria) and 10 elderly healthy controls were investigated. Cognitive performance was evaluated on the Mini Mental State Examination (MMSE) and the Brief Cognitive Rating Scale (BCRS). 3-D MRI sequences were acquired using a Siemens 1.5T scanner. Whole brain volume (WBV), total intracranial volume (TIV), volume of the frontal and temporal lobes (FL, TL) and the volume of the amygdala-hippocampus complex (AHC) were assessed using the newly developed software NMRWin. This software provides a semiautomated user independent measure of the WBV, while measurements of the substructures need to be manually guided. Measurements were performed by two independent raters (interrater reliability: $r = 0.95–0.96$, $p \pm 0.0001$) on a conventional 486 PC. As would be expected, MMSE scores were significantly ($F: 36, 98$, $p \pm 0.005$) lower in the DAT group than in the DEP group and the controls. Accordingly, we observed highly significant differences between the DEP and the DAT group for the volumes of the frontal (right FL: $F = 7.81$, $p < 0.005$; left FL: $F = 6.15$, $p < 0.005$) and temporal lobes (right TL: $F = 8.48$, $p < 0.001$; left TL: $F = 4.13$, $p < 0.05$) as well as for the AHC volume (fight AHC: $F = 23.83$, $p < 0.0001$; left AHC: $F = 30.08$, $p < 0.0001$). The TIV did not differ between the diagnostic groups. Compared to the controls, the depressed patients performed worse on the cognitive scales. However, depressed patients and healthy controls showed no significant differences in the volumetric measurements. Our results indicate that quantitative MRI may be useful to support the clinician in the differential diagnosis of depression and dementia.

MRI COMPUTER ASSISTED LINEAR BRAIN RATIOS, AND NEUROPSYCHOLOGY OF TREATMENT RESISTANT DEPRESSION IN THE ELDERLY

Steve Simpson, Bob Baldwin, Alan Jackson, Alistair Burns.

Methods: Consecutive cases of elderly DSM 111 R depression ($n = 65$), and age matched normals ($n = 24$), were assessed with a neuropsychology battery. Forty four of the depressed patients completed MRI. Simple computer assisted linear brain ratios were used as brain parameters of estimated atrophy. Response to treatment was evaluated prospectively, and patients were allocated to three

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