factor for dementia, while others show that low cholesterol may be a risk factor. The discrepant findings may be due to when cholesterol is measured over the life course (i.e., mid vs. late life) or, alternatively, relative to the progression of the underlying disease. **Objective(s):** To examine the relationship between cholesterol and dementia in a population-based cohort of women followed for 32 years. **Methods:** A total of 1,532 women from five birth cohorts born in 1908 (n=81), 1914 (n=180), 1918 (n=398), 1922 (n=464), and 1930 (n=419) were examined in 1968, 1974, 1980, 1992 and 2000. Fasting blood was drawn and cholesterol measured at each examination. Participants underwent a thorough neuropsychiatric examination and dementia was diagnosed by psychiatrists using DSM-IIIR criteria. Cox proportional hazard models were used to examine the relationship between total cholesterol and risk of dementia. Age was used as the time axis, and participants were included in the analysis from the age at which they entered the study until the age at which they developed dementia or age at the last visit or death. All models controlled for blood pressure, body mass index, education and smoking. **Results:** Cholesterol levels rose with age and then began to decline steadily after age 50-60. Over the course of the study, 161 women developed dementia. Risk of dementia was not related to concurrent cholesterol levels (aHR 1.14, 95% CI 0.97-1.33) or to maximum cholesterol levels prior to age 60 (aHR 1.13, 95% CI 0.97-1.32). However, lagging suggested there was an increased risk of dementia with higher cholesterol levels ten years or more prior to onset of disease (aHR 1.21 per mmol/dl unit increase of cholesterol, 95% CI 1.04-1.40). **Conclusions:** Timing of a cholesterol measurement in relationship to the underlying course of disease may be more important than when it is measured over the life course. High cholesterol ten or more years prior to onset of disease was associated with an increased risk of dementia. This association diminished as the disease progressed towards clinical onset.

O2-06-07 RELATION BETWEEN RETINAL MICROVASCULAR SIGNS AND CEREBRAL WHITE MATTER LESIONS: THE AGES-REYKJAVIK STUDY

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Background and Objective: Studies based on middle-aged samples have linked retinal microvascular lesions to clinical stroke and silent cerebrovascular disease. We investigated the relation of subcortical and periventricular white matter lesions (WMLs) to retinal microvascular signs in an elderly population. **Methods:** The analysis involved 1836 individuals (57.6% women) aged over 65 years who participated in the ongoing population-based Age, Gene/Environment Susceptibility (AGES)-Reykjavik study initiated in 2002. Retinal arteriovenous (A/V) nicking, focal arteriolar narrowing, and microaneurysms/retinal hemorrhages were evaluated following standardized grading protocols on digital retinal images from both eyes after pharmacologic pupil dilation. Cerebral WMLs were detected with magnetic resonance imaging and WMLs in the subcortical and periventricular regions were rated separately using validated rating scales. Multiple logistic regression models were developed to estimate the odds ratio (OR) and corresponding 95% confidence interval (CI) of retinal microvascular signs associated with subcortical and periventricular WMLs after adjusting for major potential confounders such as smoking, hypertension, diabetes mellitus, and cerebral infarcts. **Results:** The prevalence of definite retinal microvascular abnormalities in at least one eye were 30.3% for A/V nicking, 13.5% for focal arteriolar narrowing, and 17.6% for microaneurysms/retinal hemorrhages. Overall, A/V nicking was significantly associated with severity of subcortical and periventricular WMLs. Compared to the lowest quartile of WMLs, the adjusted ORs (95% CIs) of A/V nicking related to the highest quartile of subcortical WMLs were 1.64 (1.21-2.21) and periventricular WMLs were 1.69 (1.22-2.33). The association between A/V nicking and WMLs remained statistically significant or marginally significant even when both measures of subcortical and periventricular WMLs were simultaneously entered into the model. Focal arteriolar narrowing and microaneurysms/hemorrhages were associated with heavier load of periventricular WMLs, with adjusted ORs (95% CIs) for highest versus lowest quartile being 1.55 (1.01-2.38) and 1.50 (1.02-2.21), respectively. Focal arteriolar narrowing and microaneurysms/hemorrhages were not significantly associated with subcortical WMLs. **Conclusions:** Retinal microvascular lesions are correlated with load of cerebral WMLs in the elderly. This study suggests that, among the elderly population, microangiopathic changes in both retina and the brain may be concomitant.

O2-06-08 APOLIPOPROTEIN E PROFILE INFLUENCES BRAIN ACCESS BY HERPES SIMPLEX VIRUS TYPE 1

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Background: Alzheimer's disease (AD) is a devastating neurodegenerative disease of unknown etiology, where genetic and environmental factors may play a role. To date, the most important factors associated to sporadic AD are age, female gender and apolipoprotein E [ApoE]. The risk association of the APOE4 allele and AD has become almost universally accepted. Although the involvement of an infectious agent in the etiology of AD is far from fully demonstrated, Itzhaki et al. have extensively associated the herpes simplex virus type 1 (HSV-1) presence with this disease. The relative risk of developing AD for those positive for HSV-1 DNA in the brain and who carried an APOE4 allele was considerably higher than for individuals with only one (or none) of these factors. **Objective:** To analyze the effect of ApoE and gender influence on the HSV-1 infectivity to the brain, by using a model of hematogenous infection of mice. **Methods:** Wild-type, APOE knockout, APOE hemizygote, APOE3 and APOE4 humanized transgenic mice were used to analyze the influence of the ApoE on the viral loads during acute and latent infection. Moreover, male and female mice were compared. **Conclusions:** We have found that viral neuroinvasion was reduced in mice lacking ApoE at both acute and latent infection, and that the ApoE dose was directly linked to the HSV-1 cerebral concentration. The ApoE4 animals presented very high levels of virus in the brain in comparison with ApoE3 mice. In the female mice HSV-1 colonization was more effective than in males, especially in the brain. It was also found that ApoE promotes virus colonization of the ovaries, the APOE gene dose being directly related to viral invasiveness. The results presented here indicate that ApoE4 facilitates HSV-1 neuroinvasion and latency in the brain much more so than ApoE3, with ApoE dosage correlating directly with the HSV-1 cerebral concentration. Female gender presented a greater brain infection than males. Furthermore, we demonstrated the hematogenous vertical transmission of HSV-1 from maternal blood to the offspring nervous system, being also APOE-dependent. This group of data strengths the hypothesis that HSV-1 might be involved in AD.

TUESDAY, JULY 18, 2006
PLENARY
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TUESDAY PLENARY

PL-03-01 GRADUAL MEMBRANE CHOLESTEROL REDUCTION AFTER SYNAPTOGENESIS DETERMINES SURVIVAL OF HIPPOCAMPAL NEURONS IN VITRO

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Contrarily to the well-known role of survival signaling during neuronal differentiation, very little is known on how survival signaling operates during neuronal senescence. This is a most striking deficit, especially considering the stressful environment created upon the establishment of synaptogenesis (reduced oxygenation, extracellular neurotransmitter metabolite accumulation, appearance of amyloid aggregates). From this basic knowledge it appears most intuitive that neurons must possess a robust survival machinery from synaptogenesis onwards. Only this would explain the absence of dead neurons in the non-pathological aged brain. In fact, we observed that neuronal survival during senescence involves the gradual increase in activity of the TrkB/Akt pathway, starting at the time of synaptogenesis, but not earlier (implying that survival during differentiation involves a different pathway). Furthermore, suppression of Trk activity at this time, after terminal differentiation, leads to death. This type of Trk activation is ligand-independent though dependent on the small and gradual drop in the neurons' membrane cholesterol content. This lipid change is required for the oligomerization of Trk receptors into rafts where it becomes phosphorylated and induces the activation of the downstream, survival, effectors Akt/p85. Replenishment of cholesterol to the senescence neurons to the levels of differentiating counterparts results in the displacement of TrkB to non-raft domains and apoptosis while reduction of cholesterol in pre-differentiated neurons, like in the senescent counterparts, induces Trk recruitment into rafts and phosphorylation of Akt. Although most of the data reported above come from in vitro studies, embryonic rat hippocampal neurons seeded and allowed to undergo aging in primary culture conditions, the major changes, i.e. membrane cholesterol reduction, recruitment into rafts of Trk and Akt activation, were also observed in the hippocampi of two-year old mice. We can, thus, conclude that age-dependent membrane cholesterol reduction in neurons is an essential event for neuronal capacity to survive to stress. However, since membrane cholesterol functions primarily as a barrier for ion ($Na+$) leakage, it is clear that the beneficial event triggered by its loss for survival will have as a side "effect" a loss in neuronal excitability. This could explain at least some of the intellectual deficits observed during aging.

PL-03-02 LESSONS TO BE LEARNED FROM THE STUDIES IN MILD COGNITIVE IMPAIRMENT AND EARLY ALZHEIMER'S DISEASE

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Epidemiological and clinic-based studies have outlined the magnitude and extent of the cognitive problems that occur with aging. In the Canadian Study of Health and Aging an estimated 17% of individuals over age 65 were assigned a diagnosis of Cognitively Impaired Not Demented (CIND). The condition of Mild Cognitive Impairment (MCI) as described by the Mayo group is estimated to include 25-33% of patients with CIND. MCI has been reported to progress to Alzheimer's disease (AD) at annual rates of 10-15%, though in population based studies backcrossing to normal also occurs with significant frequency (43.2% / 2-years).

In the last several years, a number of large randomized clinical trials (RCTs) of MCI have been undertaken with the acetylcholinesterase inhibitors (AChEIs) donepezil, rivastigmine and galantamine, as well as with the COX-2 inhibitor rofecoxib. These studies have addressed whether the long term outcomes of MCI including conversion to the clinical diagnosis of AD could be influenced by early intervention with these pharmacological treatments. In these RCTs apparently small differences in inclusion criteria have been associated with very different rates of conversion to AD as well as rates of cognitive decline. They underscore the heterogeneity of MCI and some of the difficulties that are inherent in its use and application. The inclusion of MRI as an outcome measure has also allowed a large amount of new information on rates of decline and demonstrated the potential for discordant clinical and neuroimaging outcomes. A reconceptualization of MCI will be presented with the continued goal of allowing earlier intervention within the neurodegenerative cascade of AD.

PL-03-03 THE INFECTIOUS UNIT OF PRION DISEASES AND ITS INVASION OF NEURONAL CELLS

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A prime question is whether large protein fibrils or smaller subfibrillar oligomers are the prime causes of amyloidogenic neurodegenerative diseases. TSEs involve the accumulation of abnormal PrP, which is usually protease-resistant (PrP-res) and a major component of infectivity. Size-based fractionations of fragmented 263K PrP-res aggregates in detergent showed that non-fibrillar particles, with masses equivalent to 14-28 PrP molecules, are by far the most infectious particles per unit protein, while particles smaller than PrP hexamers had no converting activity. In scrapie-infected transgenic mice expressing PrP lacking the GPI membrane anchor, PrP-res was deposited as amyloid plaques, rather than the usual non-amyloid PrP-res. Although amyloid PrP-res induced brain damage reminiscent of Alzheimer's disease, clinical manifestations were minimal. In contrast, combined expression of anchorless and wild-type PrP gave rapid clinical scrapie. This model demonstrates the role of the PrP GPI anchor in pathogenic effects of prion diseases. To visualize the interaction between exogenous PrP-res and neuronal cells, fluorescently labeled, infectious PrP-res was used to infect neuronal cells in culture. PrP-res aggregates were internalized into intracellular vesicles and transported along neurites to points of contact with other cells, apparently by a relatively non-specific pinocytosis or transcytosis mechanism. These experiments visualize and characterize initial steps associated with scrapie infection and transport within neuronal cells.

TUESDAY, JULY 18, 2006
SYMPOSIA
S3-01
DIAGNOSIS & CLINICAL COURSE (NEUROIMAGING)

S3-01-01 MONITORING CHANGES IN BRAIN ANATOMY WITH TIME

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Background: Mapping the dynamics of grey matter (GM) loss over time in mild cognitive impairment (MCI) would be of considerable interest to assess the substrates of cognitive deterioration; capture the anatomical basis underlying conversion to clinically probable Alzheimer's disease; and monitor the effects of disease-modifying treatment on brain structure. Although ROI-based approaches are possible, only voxel-based methods can capture these dynamics across the whole brain in an unbiased and comprehensive way. Voxel-based morphometry (VBM) is particularly attractive because it allows T1-weighted MR data sets from different subjects to be merged in the same analysis, and provides statistical results in reference to Talairach's stereotactic space, i.e., allowing their probabilistic anatomical identification. However, implementing standard VBM to map longitudinal changes in gray matter volume raises issues due to the global differences impacting on the accuracy of spatial normalization. **Objectives and Methods:** We have implemented an optimized VBM method specially designed to control for global changes over time. Using this method, we mapped the progression of GM loss in 18 amnestic MCI patients over 18 months, and compared converters ($n=7$) to non-converters ($n=11$). **Conclusions:** Areas of lower baseline GM volume in converters included the hippocampus, parahippocampal cortex, and lingual/fusiform gyri. Common regions of significant GM loss over the 18-month period included the temporal neocortex, parahippocampal cortex, orbito-frontal and inferior parietal areas. However, there was significantly greater GM loss in converters in the hippocampal area, inferior and middle temporal gyrus, posterior cingulate and precuneus. These regions therefore underlie the