characteristics which differ between autopsied and non-autopsied subjects and to compare autopsy-based estimates of the frequency of neuropathological diagnoses before and after adjusting for potential verification bias. **Methods:** Subjects were all members of a Seattle-area health maintenance organization between 1987 and 1996, who presented at HMO clinics with new symptoms of previously undiagnosed dementia. Consenting subjects were enrolled in and clinically diagnosed by the UW/GHC Alzheimer's Disease Patient Registry (ADPR). Demographic and clinical characteristics were compared among clinically demented ADPR subjects who, as of October 2003, were autopsied (n = 228), had died but were not autopsied (n = 271), were still alive (n = 71), or had dropped out of the study (n = 82). Logistic regression models were used to identify characteristics associated with likelihood both of autopsy and of specific neuropathological diagnoses. Stratification on these characteristics was used to derive estimates of the frequencies of neuropathological AD and pure vascular disease, adjusted for potential verification bias. **Results:** Compared to non-autopsied subjects, autopsied subjects were more likely to be male, Caucasian, educated beyond high school, and married. They tended to have a lower baseline MMSE score and were more likely to have a clinical diagnosis of AD. Autopsy subjects also demonstrated a lower age at onset and age at study intake than subjects who died but were not autopsied. The frequency of neuropathological AD in the autopsied sample was estimated to be 64% (95% CI = 58–71%). After adjusting for verification bias, this estimate did not change substantially (60%, 95% CI = 53–66%). The frequency of neuropathological pure vascular disease (7%, 95% CI = 4–12%) also did not change appreciably after adjusting for verification bias (9%, 95% CI = 5–13%). **Conclusions:** Although demographic and clinical differences existed between autopsy and non-autopsy samples, these differences did not appreciably affect frequency estimates of several neuropathological diagnoses, suggesting that neuropathological diagnoses in the ADPR subjects provide reasonable dementia frequency estimates among ADPR patients who were clinically demented.

P2-267 A COMPARISON OF AD BRAIN PATHOLOGY FOR MEN AND WOMEN THROUGHOUT ADULTHOOD

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Background: Epidemiologic studies indicate that women are at higher risk for the development of AD compared to men. Clinical studies have not been verified by neuropathologic findings. **Objective(s):** We compared the extent of AD changes for men and women at age 25 and each decade of age thereafter to age 95. **Methods:** Information on Braak staging for SP (none, A to C) and NFT (none, I to VI) was available for more than 5000 subjects ascertained at routine autopsy. About a third of the subjects had APOE genotype information. Linear models were constructed. **Results:** There was on average over all APOE genotypes (n > 5000) a 3-year acceleration of NFT staging for women. In more detail, men and women had the same likelihood for NFT at the initial predilection site in the transentorhinal cortex (I). But, women were more likely to reach stages II (entorhinal) and III (hippocampal) clearly evident at ages 65 (p = 0.01) and 75 (p = 0.01). Isocortical stages IV to VI were also more common for women. Looking at subjects who had APOE information, there was no gender gap for APOE2/3+ subjects. There was a large gender gap for APOE4+ subjects. In addition, women at early NFT stages I to III APOE4+ and in late middle age were much more likely to have extensive SP deposits throughout the brain compared to APOE4+ men. **Conclusions:** APOE4+ women had more brain regions containing NFT and SP compared to APOE4+ men of the same age from about age 55 years onward. The rapid increase in AD neuropathology in late middle age for a subgroup of women argues in favor of development of early interventional strategies to be selectively applied and for better genetic definition of the high-risk subgroup.

P2-268 GENETICS, PATOPHYSIOLOGY AND Aβ PROTOFIBRIL FORMATION IN ALZHEIMER'S DISEASE

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Analysis of families with a distinct inheritance pattern of dementia has shown to be a powerful approach for the identification of disease genes. We have used 12 extended families with Alzheimer's disease (AD) and several hundred sib-pairs to investigate disease susceptibility regions. We performed a genome wide screen using microsatellite markers and linkage and haplotype analysis. Shared haplotypes in individual families were observed on chromosomes 2, 4 and 20. On chromosome 8 a nonparametric LOD score of 3.7 (p = 0.004) was obtained in one family. All affected individuals in this family shared a seven markers haplotype spanning approximately 50 cM. This haplotype was also found in affected individuals in other families. Amyloid β-protein (Aβ) accumulation is central in AD pathogenesis. Aβ protofibrils, an intermediate in Aβ fibril formation, have been shown to mediate neurotoxicity and disrupt neuronal electrophysiological parameters. Aβ with the Arctic mutation (Aβ E22G) enhances formation of protofibrils *in vitro*. We are investigating the fibrillization of Aβ1-42wt and Aβ1-42Arc with size exclusion chromatography by measuring decline in peaks of monomers and protofibrils. Thus, aggregation phases can be separately examined. The Arctic Aβ1-42 protofibrils forms fibrils ~18× faster than wild type protofibrils. The two phases, the monomer oligomerization and the fibrillization of protofibrils, can be influenced differently in response to physio-chemical changes. We are currently developing Aβ conformation specific monoclonal antibodies (mAb) for Aβ monomers, Aβ protofibrils and Aβ fibrils. Such monoclonal antibodies will provide an opportunity to assay these differently aggregated Aβ forms. Several mAbs have been isolated and characterized. It has been suggested that Aβ aggregates inside neurons, raising the issue whether Aβ accumulation is initiated at an intracellular, rather than extracellular, site. The Arctic mutation affects the APP processing, resulting in decreased Aβ levels as measured by ELISA, both in plasma of mutation carriers and in cell media of transfected cells. These findings has lead to the assumption that an abnormal accumulation of Aβ inside cells might occur in Arctic cells due to high levels of intracellular Aβ. Preliminary results indicate increased intracellular levels of Arctic Aβ peptides.

P2-269 HOMOCYSTEINE IS NOT ASSOCIATED WITH MEMORY AND LANGUAGE IN THE NONDEMENTED OLDEST OLD

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Background: Elevated homocysteine levels have been associated with cognitive impairment and dementia in the elderly. Few studies have examined these relationships in the oldest old. **Objective(s):** To examine the association between homocysteine levels and cognitive function in nondemented oldest old. **Methods:** 104 community dwelling nondemented (CDR = 0) subjects 85 years old and above, participating in a longitudinal study of cardiovascular risk factors for Alzheimer's disease in the oldest old, were assessed by a cognitive battery and on levels of serum total homocysteine, vitamin B12, creatinin and serum folate. **Results:** Factor analysis yielded three cognitive factors: memory (immediate recall, delayed recall, and recognition), language (fluency, shipley, and Boston), and psychomotor (digit symbol, Trails A, and Trails B). Controlling for age, education, vitamin B12, creatinin, and folate, memory (r = 0.12; p = 0.22) and language (r= −0.09; p = 0.39) performance were not significantly correlated with homocysteine level. The inverse association of homocysteine levels with psychomotor performance (r= −0.19) approached significance (p = 0.054). **Conclusions:** Elevated homocysteine levels were not associated with memory and language performance in a sample of nondemented oldest old. The trend level association with psychomotor function is consistent