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CHRONIC TRAUMATIC ENCEPHALOPATHY AND THE NATIONAL FOOTBALL LEAGUE. BI Omalu[1]. [1]Allegheny County Coroner's Office, Pittsburgh, Pennsylvania.

A report of a sentinel case of autopsy-confirmed chronic traumatic encephalopathy in a retired professional football player as a result of long term repetitive concussive brain injury. At the time of sudden and unexpected death, this retired 50 year old professional National Football League (NFL) player, was an enshrinee of the pro-football hall of fame, who had played college football, was subsequently drafted into the NFL at the age of 22 years; with a 245 game career over 17 years, principally as a startup center, and retired at the age of 39 years. Following retirement, he manifested a long-drawn clinical history of depression. A complete, post-embalmment autopsy revealed acute myocardial infarction, severe atherosclerotic coronary artery disease and dilated cardiomyopathy. The brain weighed 1565 grams and revealed no gross evidence of cortical atrophy, remote cortical contusions or remote intracranial hemorrhages. The left vertebral artery showed moderate, focal and eccentric atherosclerosis. Standard coronal sections of the brain revealed no focal gross lesions and no atrophy of the hippocampus or basal forebrain. Histologic examination revealed focal intra-mural mineralization of penetrating centrum semiovale vessels without significant neocortical neuronal dropout. Amyloid beta protein, alpha-synuclein, tau protein and neurofilament immunostains revealed frequent neocortical, diffuse amyloid plaques, many tau-positive neuritic threads and scattered neocortical neurofibrillary tangles sparing the cornu ammonis, dentate gyrus, subiculum and entorhinal cortex. Lewy bodies were absent. Many neocortical neurons revealed diffuse cytoplasmic immunopositivity for neurofilament in the perikaryon. PCR analysis of post-mortem brain tissue revealed an APOE (apolipoprotein epsilon) genotype of 3/3. Long term neurodegenerative sequelae of repeated concussive brain injury in retired professional NFL players have not yet become the focus of the NFL Committee on Mild Traumatic Brain Injury. This report constitutes a forensic epidemiological sentinel case that may justify the need for a forensic autopsy registry for retired NFL players for comprehensive tissue diagnosis and generation of empirical data on the association of professional football and long term neurodegeneration.

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GLIOBLASTOMA MULTIFORME: A STEM NEOPLASIA? R Ferracini[1], G Cenacchi[2], A Conti[1] and M Del Vecchio[1]. [1]Morbid Pathology, Bellaria Hospital, Bologna, Italy. [2]Morbid Pathology, University of Bologna, St. Orsola Hospital, Bologna, Italy.

Malignant supratentorial tumors exhibiting biphasic anaplastic populations of neurons and glia are very unusual. In a revision of a series of small cell glioblastomas, we observed five cases in which there were areas of cells positive to neuronal antigens intermingled with other areas positive to GFAP. Upon ultrastructural analysis, both areas showed cells containing aggregates of intermediated-glial filaments; other cells featured electrodense neurosecretory granules. Focally synaptic-like cytoplasmatic projections were recognizable. Hemmati et al (Proc Natl Acad Sci U S A, 2003, Nov 26) found that some brain cancers, including gliomas and medulloblastomas, can develop from cells which have many of the same characteristics as neural stem cells, but those cells have an abnormal ability to grow and change. These stem cells self renew and produce the different kinds of cells (glial, neuronal) which make up a tumor. Gene expression analysis reveals that both whole tumors and tumor-derived nanospheres express many genes characteristic of neural and other stem cells. Our data are in accord with these findings, namely, of an association between glial and neuronal ontogeny and imply that brain tumors might arise from these cells, which could be pluripotential embryonic stem cells (ESC). The ESCs form teratomas in vivo and can differentiate progenitors of neural stem cells (Noggin cells) and from them, mature neuronal and glial cells, thus linking glial and neuronal tumors. As a consequence of intra- and extracellular pathologic stimuli, these multipotential stem cells present in the adult brain undergo different genetic alterations, which produce a pure or a mixte tumor. Thinking about brain cancer as originating from these stem cells is a new way of thinking about the fundamental nature of this disease, which promises to lead to better diagnostic tests and improved cancer-specific treatments in the future.

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GENE EXPRESSION PROFILING OF PSEUDOPALISADING PERINECROTIC CELLS IN GLIOBLASTOMA. S Dong[1], CL Nutt[1], AO Stemmer-Rachamimov[1] and DN Louis[1]. [1]Department of Pathology, Massachusetts General Hospital, Boston, MA.

Palisading of tumor cells around irregular regions of necrosis (perinecrotic pseudopalisading) is a unique histological hallmark of glioblastoma. To elucidate this phenomenon at a molecular level, we microdissected populations of pseudopalisading cells surrounding necrosis and non-pseudopalisading cells from other, non-perinecrotic regions in three glioblastomas. RNA from these two populations were linearly amplified and hybridized to Affymetrix HG-U133A chips containing more than 39,000 transcript variant. The differentially expressed transcripts were identified using Vector Xpression software and further validated using GeneCluster. This approach identified 898 and 868 informative genes that were differentially ($p<0.05$) overexpressed and underexpressed, respectively, in pseudopalisades in comparison to the non-pseudopalisading cells. Of the 898 up-regulated genes, the most prominent transcripts were comprised of hypoxia-inducible genes. Some of these genes correlate with hypoxia-induced angiogenesis, whereas some reflect increased metabolism. Others may reflect the responses of tumor cells to microenvironmental stresses. The 868 down-regulated genes included transcripts related to cell adhesion and migration as well as cell proliferation. Four of the up-regulated genes and one down-regulated gene were confirmed at the protein level in a larger group of glioblastomas using immunohistochemistry. Our results suggest that the gene expression repertoire of perinecrotic pseudopalisading cells, in response to hypoxia, may facilitate angiogenesis and tumor cell invasion.

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POTENTIAL RISK FACTORS FOR GLIOBLASTOMA MULTIFORME (GBM): DATA FROM THE HONOLULU HEART PROGRAM/HONOLULU ASIA AGING STUDY (HHP/HAAS). JS Nelson[1], CM Burchfiel[2], RD Abbott[3], D Fekedulegn[2] and ME Andrew[2]. [1]Pacific Health Research Institute, Honolulu, HI. [2]Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Morgantown, WV. [3]Division of Biostatistics and Epidemiology, University of Virginia School of Medicne, Charlottesville, VA.

The HHP began in 1965 as a longitudinal study of cardiovascular disease and stroke among 8006 men of Japanese ancestry, 45 to 68 years of age, living on the island of Oahu. Investigation of neurodegenerative disease in surviving participants began in 1991 with the HAAS. Since 1965 the cohort has been followed through 6 standardized examinations with follow up on all hospitalizations and mortality through surveillance of hospital and death records. Medical histories, physical measurements, laboratory values, demographic, socioeconomic, and lifestyle data collected at the first three examinations, 1965 through 1974, were used for this study. Measurement of risk factors before onset of clinical disease provides risk estimates based on exposure status. Between 1965 and 1998, 9 participants, 58 to 80 years old, developed GBM, an incidence of 6.2/100,000 person-years. All cases were histologically confirmed. Analysis of a large number of potential risk factors showed GBM cases were associated with increased dietary glucose and carbohydrate levels, low alcohol consumption including wine, and solvent exposure, especially carbon tetrachloride. Incidence rates tended to be higher with increasing adiposity and serum cholesterol levels. No associations were observed with blood pressure, heart rate, pulmonary function, Japanese diet, recurrent herpes labialis, medication use for diabetes or hypertension, smoking, and pesticide or metal exposure. The previous reports of GBM risk with chlorinated aliphatic hydrocarbon exposure are supported. Dietary glucose and carbohydrate risk may be related to acrylamide formation during food preparation. The database of a non-neoplastic epidemiological study may be used to identify potential GBM risk factors.

AMERICAN ASSOCIATION OF NEUROPATHOLOGISTS

Abstracts of the

80th ANNUAL MEETING

June 24–27, 2004

Cleveland, Ohio
Renaissance Cleveland Hotel

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THE HISTONE DEACETYLASE INHIBITOR TRICHOSTATIN A AMELIORATES MURINE EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS, A MODEL OF MULTIPLE SCLEROSIS. S Camelo[1,2,3], AH Iglesias[1], D Hwang[4], B Due[1], SG Gray[1], J Imitola[1], G Duran[1], B Langley[5], MP Frosch[6], SJ Khoury[1], G Stephanopoulos[4], RR Ratan[5], U DeGirolami[1], RJ Ferrante[2,3] and F Dangond[1]. [1]Brigham and Women's Hospital, Boston, MA. [2]Edith Nourse Veteran's Hospital, Bedford, MA. [3]Boston University, School of Medicine, Boston, MA. [4]Massachusetts Institutes of Technology, Cambridge, MA. [5]Beth Israel Deaconess Medical Center, Boston, MA. [6]Massachusetts General Hospital, Boston, MA.

Multiple sclerosis (MS) is an inflammatory and demyelinating disease of the central nervous system in which there is neuronal and axonal loss. Experimental autoimmune encephalomyelitis (EAE), a T helper 1 (Th1) cell-driven disease, is a model of MS. Histone deacetylase inhibitor (HDACi) drugs, such as Trichostatin A (TSA), are known to block Th1 cytokine expression. We administered TSA to EAE induced mice and analyzed its clinical and molecular efficacy. EAE was induced in 6-8 weeks old female C57BL/6 mice using myelin oligodendrocyte glycoprotein (35-55). The animals were then treated with either TSA 7.5mg/kg/d i.p. (n=24) or its solvent as a vehicle (n=25) from day 4 to 40. Disability was scored on a scale from 0-5. There were no differences in mean day of disease onset between groups. However, TSA-treated mice had reduced clinical disability with a significant drop in both the mean peak of remission phase ($p=0.004$) and the Disease Index calculated at day 40 (360.6) as compared to vehicle (482.7). Mice were sacrificed on day 40 for tissue analysis. Spinal cords from TSA-treated animals had a decrease of inflammatory infiltrates, demyelination, and axonal loss. Stereological analysis revealed a significantly greater preservation of spinal cord tissue volume ($p<0.001$) and neuronal cell number ($p<0.01$) in the TSA-treated EAE mice. TSA treatment induced spinal cord anti-oxidant, anti-excitotoxicity, and pro-survival gene expression. TSA also led to an increase in spleen transforming growth factor 1 (TGF-beta1) and a decrease in splenocyte tumor necrosis factor alpha (TNF-alpha), macrophage inflammatory protein 2 (MIP-2), and E2F1 proteins. We conclude that TSA has both anti-inflammatory and neuroprotective roles that lead to clinical amelioration of the chronic phase of EAE. Our findings suggest that a transcriptional imbalance leading to immune dysregulation and neurodegeneration may contribute to the pathogenesis of EAE. This suggests that HDACi drugs may provide clinical benefit to MS patients

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PATHOLOGIC CORRELATIONS OF MRI ''DIRTY-APPEARING WHITE MATTER'' IN MULTIPLE SCLEROSIS. GRWayne Moore[1,2], C Laule[3], AL MacKay[3,4,5], E Leung[2], DKB Li[4,5], G Zhao[4], A Traboulsee[6,7,8] and DW Paty[6,7,8]. [1]Department of Pathology and Laboratory Medicine, Vancouver General Hospital, Vancouver, BC, Canada. [2]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada. [3]Department of Physics and Astronomy, University of British Columbia, Vancouver, BC, Canada. [4]Department of Radiology, University of British Columbia, Vancouver, BC, Canada. [5]Department of Radiology, Vancouver General Hospital and UBC Hospital, Vancouver, BC, Canada. [6]Department of Medicine (Neurology), Vancouver General Hospital and UBC Hospital, Vancouver, BC, Canada. [7]Department of Medicine (Neurology), University of British Columbia, Vancouver, BC, Canada. [8]Multiple Sclerosis Clinic, UBC Hospital, Vancouver, BC, Canada.

It is now recognized that there are a number of abnormalities in non-lesional multiple sclerosis (MS) white matter, which appears normal on gross examination and by routine diagnostic MRI and is referred to as ''normal appearing white matter'' (NAWM). More recently, areas of subtle changes in non-lesional MS white matter have been detected on T2-weighted MRI. These show an intensity intermediate between lesions and NAWM and are referred to as ''dirty-appearing white matter'' (DWM). The purpose of this study was to determine the pathologic correlate of DWM in terms of myelin and axonal pathology. For this, archival formalin-fixed slices of cerebral hemispheres of 4 cases of chronic MS (3 with DWM and 1 without DWM) were scanned on 1.5T MRI scanner employing multi-echo T2-weighted imaging and T2 relaxation measurements from which a short T2 component has previously been shown to correlate with myelin content, allowing us to create a myelin water image map. 10 um-thick paraffin sections from 5 levels through the 3mm slice of hemisphere scanned were stained with Luxol fast blue (LFB), Bielschowsky stain and immunocytochemically for myelin basic protein (MBP) and 2', 3'-cyclic nucleotide 3'-phosphohydrolase (CNP). The T2 relaxation results showed reduced myelin water content in the region of the DWM. Areas of reduced LFB-staining correlated well with the DWM areas, which did not show as severe loss of staining as plaques. There was reduction in Bielschowsky staining in DWM, but not nearly as severe as the LFB loss. In 2 of the cases with DWM and in the case without DWM, staining for MBP, and to a much lesser extent CNP, showed mild but wide-spread reduction in staining involving most of the hemispheric white matter with relative sparing of subcortical u-fibres. In summary, this study has shown that, in addition to widespread abnormalities evident in MS-NAWM as reflected in diffuse loss of MBP, there is also significant myelin loss and axon loss in DWM, with the myelin loss being the more prominent feature. The clinical prevalence and significance of these findings warrants further investigation. (Supported by the Multiple Sclerosis Society of Canada and Berlex).

All presenters have disclosed that they have no commercial interests unless otherwise specified under the individual abstracts.