G103 Increased Risk of Sudden Infant Death Syndrome (SIDS) Among Infants Harboring the Apolipoprotein E-4 Allele: Genetic and Pathologic Similarities to Alzheimer's Disease (AD)

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After attending this presentation, attendees will learn that there is increased apoptotic neurodegeneration in SIDS, which may constitute the proximate cause of death, and that similar to AD, the risk of SIDS may be enhanced among those individuals harboring the Apolipoprotein E-4 allele.

Because of the 96% incidence of increased numbers of Alz-50 immunoreactive neurons in SIDS, this microscopic feature may be useful in establishing the criteria for an objective diagnosis, if convincingly confirmed. This presentation will impact the forensic community and/or humanity by providing direction for future investigation, along the lines of altered cholesterol metabolism in SIDS, and the relationship between the severity of Alz-50 pathology and dose of the ApoE-4 allele.

Introduction: A number of studies suggest a neuropathologic overlap between Sudden Infant Death Syndrome (SIDS) and the dementing disorder Alzheimer's disease (AD). AD is a neurodegenerative disease characterized by the pathologic presence of neurofibrillary tangles and accumulation of the peptide β-amyloid, predominantly in the temporal cortex and hippocampus. Pre-tangles (early form of the neurofibrillary tangle) and degenerating neurons in AD and increased numbers of neurons in SIDS medulla and temporal cortex are reactive with Alz-50 antibody compared to respective control populations. Likewise, increased levels of the neurotoxin β-amyloid are uniformly present in AD brain and have been observed in the temporal lobe of many SIDS infants. Studies of nondemented individuals with coronary artery disease (CAD) suggest that Alz- 50 immunoreactive neurons occur in advance of AD-like β-amyloid accumulation. An increased risk of developing AD is associated with increased frequency of the Apolipoprotein E-4 (ApoE-4) genotype. Three ApoE alleles taken two at a time are possible (2/2, 2/3, 3/3, 2/4, 3/4 and 4/4). Likewise, there is an increased risk of CAD if an individual retains the ApoE-4 genotype, reportedly because of associated elevations in circulating cholesterol levels. Elevated circulating cholesterol is prevalent in AD and cholesterol is emerging as a factor promoting production of β-amyloid in the disorder. Furthermore, CAD in early life increases the risk of developing AD.

Scientific Objectives: (1) Determine if there is increased prevalence of the ApoE-4 genotype among infants dying of SIDS compared to agematched infants dying of known causes; (2) Provide previously published data indicating that Alz-50 antibody highlights neurons undergoing apoptosis; (3) Demonstrate that there are significantly increased numbers of Alz-50 immunoreactive neurons throughout the length of the respiratory nuclei in the medulla of SIDS infants, thus suggesting that neurodegeneration may underlie the cause of SIDS.

Methods: The authors investigated 115 infants > 4 weeks of age and < 12 months of age (81 SIDS and 34 non-SIDS) for ApoE genotype. The cause of death was diagnosed using 1991 NICHD criteria for SIDS and standard protocols for known causes (non-SIDS). ApoE-4 genotype was evaluated in brain tissue using real-time PCR methods. Temporal cortex and medulla from a subset of these infants were evaluated for Alz-50 immunoreactive neurons in 50 µm vibratome sections. Some sections were counterstained for condensed DNA (apoptotic bodies) with propidium iodide subsequent to Alz-50 immunohistochemistry and RNAase treatment (to degrade all RNA).

Results: The mean age at death was 94.5 + 7.8 days among infants with the E-4 allele and 93.2 + 12.4 days among infants without the E-4 allele. The ApoE-4 allele occurred in 29.95% of the infant population and was absent in 70.15% of the infants. The ApoE-4 allele frequency was increased in SIDS (16.75%) compared to infants dying of known causes (7.6%); this difference was significant using the Armitage's trend test ($P < 0.05$) and marginally significant ($P = 0.086$) using a linear-by-linear chi square assessment. There was a 2.2-fold increased risk of SIDS (OR, 0.76 – 6.46) if an infant harbored the ApoE-4 allele.

Ninety-six percent of SIDS infants exhibit significantly greater numbers of Alz-50 immunoreactive neurons in temporal lobe and throughout the extent of, and exclusively in the dorsal and ventral respiratory nuclei and the reticular activating nuclei of, the dorsal medulla. Essentially all Alz-50 immunoreactive neurons in SIDS brain exhibit condensed bodies of DNA stained by propidium iodide (apoptotic bodies). Such apoptotic bodies were confined to the nuclear envelope and did not occur in the

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absence of an Alz-50 immunoreactive neuron.

Discussion: There is a greater than 2-fold increase in the ApoE-4 allele frequency among infants dying of SIDS compared to age-matched infants dying of known causes. This is similar to the just over 2-fold increase in the ApoE-4 genotype among individuals with AD compared to age-matched non-demented non-heart disease controls. This genetic difference in SIDS is concomitant with a marked increase in features suggestive of early AD neuropathology. Because of the anatomic link between the location of enhanced apoptosis in the medulla and control of involuntary respiration and arousal from sleep, SIDS may be a neurodegenerative disorder of infancy. Future multi-site studies will be required to confirm this possibility. Due to the link between ApoE genotype and cholesterol metabolism, investigation of cholesterol levels in SIDS brains and circulation may be fruitful.

Conclusions: SIDS may be the AD of infancy, and as in AD, the influence of ApoE genotype may contribute to the severity of neuropathology in SIDS.

SIDS, Alzheimers-Like Neuropathology, Apolipoprotein E Genotype

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