

**EVIDENCE OF PROGRESSIVE PATHOGENESIS IN THE BRAINS OF COMPARATIVE NORMATIVE CONTROL SAMPLES IN AN ALZHEIMER DISEASE STUDY.**

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Tissue samples from aging normative brains are rarely Alzheimer's disease (AD) lesion burden free. In this study we investigate the AD lesion burden within comparative normative (NM) brain samples used in a study investigating the pathogenesis of AD. Quantitative data which included counts of NFTs, SPs, and capillaries immuno-stained for VEGF, eNOS, LRP, RAGE and P-gp from comparable and 10 randomly selected superior temporal site samples in each of 14 normative brains. The samples were taken from 8 female and 6 male brains aged 63 to 80 years. For the purposes of this study the brains were divided into two groups: those with less than 2 NFTs and / or 4 SPs (*low lesion*); and those with more of either lesion (*high lesion*). Our results demonstrate that there is a significant difference between the two groups and that the high lesion group results were quantitatively higher in every observation category (p 0.01 or less). Both LRP and P-gp expression levels were significantly negatively correlated to both NFT and SP burdens (p 0.05 or less). These results point towards underlying pathogenic blood-brain barrier microvascular alterations and dysfunction in normative brains and, further, are supportive evidence for progressive AD lesion pathogenesis in aging normative brains.