Age-related cytoskeletal pathologies

6.3 Societal Impact

Our neuropathological evidence in elderly Sri Lankan brains indicates a higher prevalence of Parkinsonism associated pathologies (8·51%) followed by AD (4·25%). It urges the neuroscientific body in Sri Lanka to continue further investigations based on genetic susceptibility, environmental exposures and the dietary patterns which are unique to this region. Vascular burden in brain aging and its coexistence in the manifestation of AD-related neuropathological changes are highly focused in this study. We demonstrated that besides age, education, and genetic factors such as *ApoE ε4* alleles and *MTHFR T* alleles, other vascular risk factors were not associated with AD-related neuropathological changes. Moreover, cerebral small vessel pathologies such as WMHs and CAA were identified as potential coexisting cerebrovascular changes in the etiology of sporadic AD. We further emphasize that consumption of natural products that contains anti-amyloidogenic components and folic acid supplementations could be used as preventative strategies against these pathologies. Large vessel pathology, atherosclerosis of the CW did not show any significant associations with AD-related neuropathological changes, thus interrogates vascular hypothesis in the etiology of sporadic AD which was proposed on intracranial atherosclerosis of the CW, a major cause for cerebral hypoperfusion. We suggest that CW atherosclerosis might contribute to vascular cognitive impairment rather than sporadic AD.

Differences in *ApoE* allelic frequencies and their carriers' survival probabilities could possibly be the main reasons for the variations observed in sporadic AD prevalence among population-based studies. Age-based risk of NFTs, *ApoE ε4* allele-based risk of Aβ plaques and the survival probabilities of *ApoE ε4* allele carriers may cause discordance between NFT and Aβ plaque stages in AD neuropathological diagnosis. Our observations support the inapplicability of NIA-RI criteria on AD research settings. Similarly, *ApoE ε2* and *ε4* allelic frequencies and their carriers' survival probabilities could possibly be the main reasons for the discrepancies observed between posterior and anterior circulation atherosclerotic stroke incidence in population-based studies. In our study, subjects with *ApoE ε3/ε4* genotype showed an increased risk of severe atherosclerosis in posterior circulation whereas subjects with *ApoE ε3/ε2* genotype showed reduced risk of atherosclerosis in anterior circulation. We also reported some novel findings such as significant associations obtained between sporadic CAA and *MTHFR C677T* polymorphism, and between hypoplastic CW component arteries and microscopic infarcts in deep white matter. However, large-scale neuropathological studies in ageing brains are recommended. We further demonstrated that early AD-related neuropathological changes may contribute sufficiently to elderly injury deaths caused by traffic accidents. This is a serious public health issue in Sri Lanka as well as in other low- and middle-income countries; however, it has not been taken into consideration by the government or healthcare systems. We suggest that forensic autopsy should include neuropathological examination in elderly injury deaths caused by fatal accidents. Further, it is important to have an awareness of a possible link between cognitive impairment or early stages AD and cause of death in the elderly. This provides an opportunity to reduce the risk of injury deaths in this age group.

There are no cures for dementia caused by progressive neurodegenerations including AD and LBD. A better understanding of dementia causes, as well as their diagnosis and treatment, will make it possible for affected individuals and their caretakers to live and meet their daily challenges mostly. It is an urgent requirement to develop cost effective packages of medical and social care that fulfills affected individuals and their caretakers need throughout the course of illness. Government and health care systems need to be prepared adequately for future and must seek the possible ways to improve their quality of lives. Only by investing now in research and cost-effective approaches to early diagnosis and care can future societal costs be anticipated and managed.