

Early stages of Alzheimer's disease are alarming signs in injury deaths caused by traffic accidents in elderly people (≥ 60 years of age): A neuropathological study

Printha Wijesinghe, Catherine Gorrie¹, S. K. Shankar², Yasha T. Chickabasaviah², Dhammika Amaratunga³, Sanjayah Hulathduwa⁴, K. Sunil Kumara⁵, Kamani Samarasinghe⁶, Yoo-Hun Suh⁷, H. W. M. Steinbusch⁸, K. Ranil D. De Silva

Department of Anatomy, Faculty of Medical Sciences, Genetic Diagnostic Research Laboratory and Human Brain Bank Tissue Repository, University of Sri Jayewardenepura, Nugegoda, Sri Lanka, Departments of ⁴Forensic Medicine and ⁶Pathology, Faculty of Medical Sciences, University of Sri Jayewardenepura, Nugegoda, ⁵Department of Judicial Medical Office, Colombo South Teaching Hospital, Colombo, Sri Lanka, ²Nonclinical Biostatistics, Janssen Research and Development (Retired), Raritan, USA, ¹School of Medical and Molecular Biosciences, University of Technology Sydney, Sydney, Australia, ³Department of Neuropathology, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India, ⁷Department of Pharmacology, College of Medicine, Seoul National University, Seoul, South Korea, ⁸Department of Translational Neuroscience, Faculty Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands

ABSTRACT

Background: There is little information available in the literature concerning the contribution of dementia in injury deaths in elderly people (≥ 60 years).

Aim: This study was intended to investigate the extent of dementia-related pathologies in the brains of elderly people who died in traffic accidents or by suicide and to compare our findings with age- and sex-matched natural deaths in an elderly population.


Materials and Methods: Autopsy-derived human brain samples from nine injury death victims (5 suicide and 4 traffic accidents) and nine age- and sex-matched natural death victims were screened for neurodegenerative and cerebrovascular pathologies using histopathological and immunohistochemical techniques. For the analysis, Statistical Package for the Social Sciences (SPSS) version 16.0 was used.

Results: There was a greater likelihood for Alzheimer's disease (AD)-related changes in the elders who succumbed to traffic accidents (1 out of 4) compared to age- and sex-matched suicides (0 out of 5) or natural deaths (0 out of 9) as assessed by the National Institute on Aging – Alzheimer's Association guidelines. Actual burden of both neurofibrillary tangles (NFTs) and (SPs) was comparatively higher in the brains of traffic accidents, and the mean NFT counts were significantly higher in the region of entorhinal cortex ($P < 0.05$). However, associations obtained for other dementia-related pathologies were not statistically important.

Address for correspondence: Prof. K. Ranil D. De Silva, Department of Anatomy, Faculty of Medical Sciences, Genetic Diagnostic and Research Laboratory and Human Brain Bank Tissue Repository, University of Sri Jayewardenepura, Nugegoda 10250, Sri Lanka.
E-mail: ranil@sjp.ac.lk

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Conclusion: Our findings suggest that early Alzheimer stages may be a contributing factor to injury deaths caused by traffic accidents in elderly people whereas suicidal brain neuropathologies resembled natural deaths.

Key words: Alzheimer-related pathologies, immunohistochemistry, injury deaths, natural diseases

INTRODUCTION

Unnatural causes of death among elderly people on medicolegally examined autopsies have not been studied extensively. Accidents are the main causes of injury deaths among the elderly followed by suicide, whereas homicide is a rare or uncommon cause of injury death among these people.^[1,2] To date, there have been no studies compared the extent of dementia-related pathologies in the brains of elderly people who died of injuries and natural diseases. There is a small number of studies from Western countries which investigated the extent of dementia-related pathologies in the brains of elderly victims of suicide^[3-6] and fatal traffic accident brains.^[7-9] Autopsy findings, however, were inconclusive. Primary objective of this study was to determine whether there is an over-representation of Alzheimer-related pathologies in the brains of elders (≥ 60 years) who succumbed to injury deaths caused by traffic accidents and suicide and to compare it with the brains of elders (≥ 60 years) who died of natural diseases.

MATERIALS AND METHODS

Human brain samples were obtained at autopsy from 18 elderly subjects (≥ 60 years) at the Department of Judicial Medical Office, Colombo South Teaching Hospital, following approval by the Institutional Scientific Ethics Committee to carry out the study and informed consent from kin. Among these samples, nine brains were from injury deaths – five suicide victims and four fatal traffic accident victims (mean age 74.8 years [7.3], mean age [standard deviation]; male:female = 5:4) – and nine brains from natural deaths (mean age 74.8 years [7.6]; male:female = 5:4). Brains of other injury deaths, including falls, drowning, war, adverse outcome of surgery, and homicide, were not obtained during this period. As this study was a retrospective study, an ante-mortem questionnaire was given to kin who were familiar with intellectual and motor functional status of the subjects before death. The purpose of this questionnaire was to obtain information on demographic data, medical history, family history, and health habits of the deceased. This information was held strictly confidential. All the recruited cases had incomplete clinical history, except one case which was clinically diagnosed as Parkinson's disease (PD). Specific neuroanatomical regions were sampled for paraffin embedding and sectioning from both hemispheres: hippocampus along with parahippocampal gyrus, superior frontal gyrus, middle temporal gyrus,

superior parietal lobule, midbrain at superior colliculus level and deep white matters from corpus callosum-major inter-hemispheric white matter tract, and the circle of Willis (CW) for the subsequent atherosclerotic study.

Following routine histological evaluation (H and E), formalin-fixed paraffin-embedded brain sections were immunostained by standard immunoperoxidase technique following antigen retrieval by heat and DAB/H₂O₂ as the chromogen to visualize the immunolabeling (DAKO Envision Detection System). For this screening, three antibodies, namely, (i) β -amyloid (A β) – monoclonal antibody (1:200 dilution) from Novacastra™, (ii) ubiquitin – monoclonal antibody (1:150 dilution) from Novacastra™, and (iii) phosphorylated tau – paired helical filament (PHF) – 1 monoclonal antibody (1:50 dilution, A gift) were used. Phosphorylated tau- and A β -positive pathologies were graded semiquantitatively as given below.

1. Semi-quantitative 0–3 scale (0 - none, + - low, ++ - moderate, and +++ - high) for tau-positive neurons (neurons demonstrating tangle and pretangle pathology), neuritic plaques (NPs), and neuropil threads (NTs)
2. Semi-quantitative 0–3 scale (0 - none, + - sparse, ++ - moderate, and +++ - frequent) for A β -positive senile plaques (SPs – dystrophic neurites and an amyloid core) and diffuse plaques (DPs).

The diagnostic criteria for Alzheimer's disease (AD) neuropathologic change was based on National Institute on Aging – Alzheimer's Association guidelines (NIA-AA)^[10] – a practical approach which included:

- Consortium to Establish a Registry for AD (CERAD) protocol for NP scoring^[11]
- Braak and Braak staging scheme for neurofibrillary tangle (NFT) degeneration^[12,13] which was adapted to four stages that improve inter-rater reliability (stage 0, stage I or II, stage III or IV, and stage V or VI)^[14]
- A modified version of Thal phases for A β plaque accumulation^[15] which was adapted to four-point scale (phase 0, phase 1 or 2, phase 3, and phase 4 or 5).

AD neuropathologic change was ranked by three parameters: A β plaque phase, Braak and Braak NFT stage, and CERAD NP score to obtain ABC scores and then transformed into four levels: not, low, intermediate, or high.^[10] Actual burden of AD-related pathologies (NFTs and SPs) were counted in specific brain regions such

as hippocampus, parahippocampus, superior frontal gyrus, and midbrain based on the methods described by Purohit *et al.*^[16] For this purpose, a medium high power ($\times 20$) objective lens producing a visual field of 0.785 mm² (field diameter = 2.0 mm) was used. Lesions were counted in medium high ($\times 200$, Olympus U-CTR30-2 Trinocular objective tubes and $\times 10$ eye piece) power fields and then converted into average per $\times 200$ as follows: for superior frontal gyrus, areas with high NFTs/SPs were selected and visual counts were carried out in five nonoverlapping fields. For other regions, areas with high NFTs/SPs were identified in each subfield and then visual counts were carried out in nonoverlapping fields (wherever possible five nonoverlapping fields were selected).

Neuropathological criteria for Lewy body diseases (LBDs) including PD and dementia with Lewy bodies (DLBs) were based on NIA-AA^[10] modifications to existing criteria which included Consortium on DLBs 2005 (CDLB05)^[17] and Braak PD staging^[18] system. To detect Lewy bodies, α -synuclein immunohistochemistry is recommended as a preferred method; however, in this study, H and E staining and ubiquitin immunohistochemistry which were recommended in CDLB 1996 criteria^[19] were used. Cerebral amyloid angiopathy (CAA) in leptomeningeal and cortical arteries of the specific neuroanatomical regions was graded based on Greenberg and Vonsattel^[20] specifications and the average CAA grade was reported for each case. Intracranial atherosclerosis of the CW (IASCW) was graded into four levels: none, mild, moderate, and severe based on the degree of stenosis of the CW component arteries^[21] and the gross visual inspection (macroscopic grading).^[22] Extent of other cerebrovascular pathologies: microscopic infarcts in deep white matters (7 μ m thick) stained with Luxol fast blue (LFB) and cresyl violet and white matter hyperintensities (WMHs) in the neocortex and hippocampus regions stained with LFB and eosin were assessed semi-quantitatively as absent (none/rare) and present (above levels). Due to the high variability of

morphological findings and multifactorial pathogenesis of vascular cognitive impairment/vascular dementia (VaD),^[23-26] no generally accepted morphologic scheme for quantitating vascular brain injury and no validated neuropathological criteria for VaD have been established to date.^[25,26] On the whole, the basis of VaD diagnosis is simply the presence of brain lesions related to vascular pathology and it highly depends on the neuropathologist's judgment.

Statistical analysis

Results were analyzed using statistical software SPSS for windows version 16.0, SPSS Inc., Chicago, USA. Mann–Whitney U-test was used to find the differences in AD-related neuropathological scores in different brain regions among injury deaths caused by traffic accidents and suicide and natural deaths.

RESULTS

This sample consisted of 18 deceased brains aged between 60 and 87 years. The mean age between traffic accidents (78.7 years [3.1]) and natural (78.5 years [3.2]) deaths; suicide (71.6 years [3.4]) and natural deaths (71.8 years [3.2]); and traffic accidents (78.7 years [3.1]) and suicide (71.6 years [3.4]) was not significantly different ($P > 0.05$, Mann–Whitney U-test). Sample summary on AD, LBD, and CAA neuropathological stages is given in Table 1. Among these samples, AD neuropathologic change for intermediate level considered as greater likelihood for dementia or cognitive impairment was found only in one out of four traffic accidents and for low level considered as inadequate evident was found in one out of four traffic accidents, one out of five suicides, and two out of nine natural deaths.

Figure 1 illustrates the percentage of cases identified with AD-related and cerebrovascular pathologies among injury and natural deaths. AD-related pathologies; Braak NFT stage, Thal A β phase, and CERAD NP score were comparatively

Table 1: Sample summary on Alzheimer's disease, cerebral amyloid angiopathy, and Lewy body disease neuropathological stages

Sample size	Braak and Braak NFT stage	CERAD NP score	Thal A β phase	NIA-AA (criteria)	CAA grade	LBD stage
Traffic accidents (4 cases)	None 0% Stage I-II 50.0% (2/4) stage III-IV 50.0% (2/4)	None 75.0% (3/4) Stage B 25.0% (1/4)	None 50.0% (2/4) Phase 1-2 50.0% (2/4)	Not 75.0% (3/4) Low 25% (1/4) Intermediate/ high 25.0% (1/4)	None 50.0% (2/4) Grade 1 25% Grade 2 25%	None 100.0% (4/4)
Suicide (5 cases)	None 0% Stage I-II 60.0% (3/5) stage III-IV 40.0% (2/5)	None 80.0% (4/5) Stage B 20.0% (1/5)	None 80.0% (4/5) Phase 1-2 20.0% (1/5)	Not 100.0% (5/5) Low 20% (1/5)	None 80.0% (4/5) Grade 1 20.0% (1/5)	None 80.0% (4/5) Brain stem-predominant-20.0% (1/5)
Natural deaths (9 cases)	None 11.1% (1/9) stage I-II 55.56% (5/9) Stage III-IV 33.3% (3/9)	None 100.0% (9/9)	None 77.78% (7/9) Phase 1-2 22.2% (2/9)	Not 100.0% (9/9) Low 22.2% (2/9)	None 88.89% (8/9) Grade 1 11.1% (1/9)	None 100.0% (9/9)

CAA – Cerebral amyloid angiopathy; LBD – Lewy body disease; CERAD NP – Consortium to establish a registry for Alzheimer's disease protocol for neuritic plaque; A β – Amyloid; NIA-AA – National Institute on Aging – Alzheimer's association; NFT – Neurofibrillary tangles; NP – Neuritic plaques

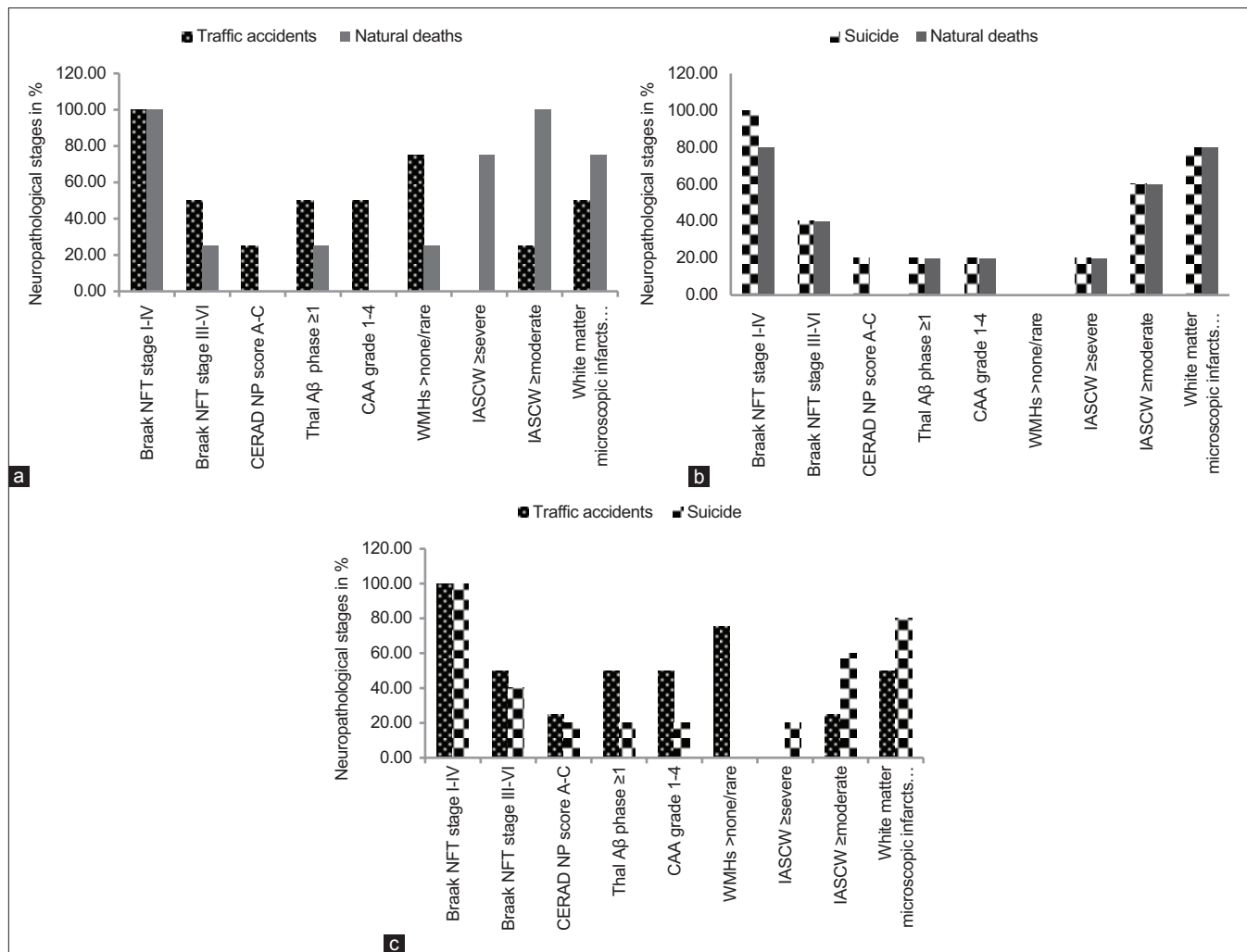


Figure 1: (a-c) Alzheimer and cerebrovascular neuropathological stages among injury deaths caused by traffic accidents and suicide and natural deaths. NFT – Neurofibrillary tangle; Aβ – β-amyloid; CERAD – Consortium to Establish A Registry for Alzheimer's disease; NP – Neuritic plaque; CAA – Cerebral amyloid angiopathy; WMHs – White matter hyperintensities; IASCW – Intracranial atherosclerosis of the circle of Willis

higher in traffic accidents compared to suicide or natural deaths. CAA and WMHs, which are most frequent coexisting cerebral small vessel diseases in the AD brains, were also identified prominently in the brains of traffic accidents. In contrast, large vessel pathologies; IASCW and white matter microscopic infarcts were identified prominently in natural deaths.

Association between cause of death and actual burden of AD-related pathologies is presented in Table 2. Mean counts of both NFTs and SPs were comparatively higher in the brains of traffic accidents compared to suicide or natural deaths. In particular, mean NFT counts were significantly higher ($P < 0.05$) in the region of entorhinal cortex. Figure 2 illustrates the hallmark lesions of AD including tau-positive NFTs and NPs, and Aβ-positive SPs observed in the brains of injury deaths. One among the 05 suicidal victims who had clinically diagnosed of PD presented brainstem-predominant Lewy bodies (stage 3) at neuropathological diagnosis.

DISCUSSION

Our study demonstrates a trend in elderly brain neuropathology where AD-related pathologies are predominant in injury deaths caused by traffic accidents, whereas large vessel pathologies; IASCW and microscopic infarcts are predominant in natural deaths and also in suicide. There is a significant overrepresentation of NFTs identified in the region of entorhinal cortex, the first area of the brain to be affected in AD.^[27] Therefore, our results suggest that early AD-related neuropathological changes may contribute sufficiently to elderly injury deaths caused by traffic accidents by affecting their cognitive status. For this screening, we have used the recent NIA-AA guidelines – a practical approach^[10] to assess the neuropathological changes related to AD and LBDs. NIA-AA recommends immunohistochemistry as the most preferred methodology to screen AD-related pathologies and it was followed in this study (β-amyloid for Aβ plaques, phosphorylated tau for Braak and Braak NFT stages, and

Table 2: Actual burden of Alzheimer related pathologies among injury deaths caused by traffic accidents and suicide, and natural deaths

Regions	Lesions	Traffic accidents (count/mm ²) mean±SE (n=04)	Natural deaths (count/mm ²) mean±SE (n=04)	P	Suicide (count/mm ²) mean±SE (n=05)	Natural deaths (count/mm ²) mean±SE (n=05)	P	Traffic accidents (count/mm ²) mean±SE	Suicide (count/mm ²) mean±SE	P
Age	-	78.75±3.12	78.50±3.17	0.883	71.60±3.41	71.80±3.25	0.916	78.75±3.12	71.60±3.41	0.221
Hippocampus	NFTs	57.23±34.0	23.08±14.57	0.386	29.87±15.99	18.63±11.05	0.754	57.23±34.0	29.87±15.99	0.327
	SPs	4.12±2.42	0.00±0.00	0.131	1.33±1.33	0.00±0.00	0.317	4.12±2.42	1.33±1.33	0.244
Entorhinal cortex	NFTs	22.56±6.48	2.54±1.50	0.021*	6.11±3.75	20.65±9.31	0.754	22.56±6.48	6.11±3.75	0.050*
	SPs	4.40±2.88	0.00±0.00	0.131	0.97±0.97	0.00±0.00	0.317	4.40±2.88	0.97±0.97	0.244
Superior frontal gyrus	NFTs	0.60±0.45	0.06±0.06	0.321	0.15±0.10	0.00±0.00	0.136	0.60±0.45	0.15±0.10	0.500
	SPs	2.69±2.21	0.00±0.00	0.131	1.94±1.94	0.20±0.20	0.881	2.69±2.21	1.94±1.94	0.561
Midbrain	NFTs	5.12±2.22	3.33±2.28	0.386	1.01±0.51	4.84±1.95	0.116	5.12±2.22	1.01±0.51	0.140
	SPs	0.13±0.13	0.00±0.00	0.317	0.00±0.00	0.00±0.00	1.000	0.13±0.13	0.00±0.00	0.264
All regions	NFTs	85.51±36.90	29.02±15.92	0.248	37.15±14.51	44.12±16.40	0.917	85.51±36.90	37.15±14.51	0.142
	SPs	11.34±6.59	0.00±0.00	0.131	4.23±4.23	0.20±0.20	0.881	11.34±6.59	4.23±4.23	0.383
Cortical and leptomenigeal regions	CAA	2.25±1.31	0.00±0.00	0.131	0.60±0.60	1.20±0.80	0.521	2.25±1.31	0.60±0.60	0.244

P values are calculated using Mann-Whitney U test and the significant levels are presented at * $P < 0.05$. SE – Standard error; n – Number of cases; NFTs – Neurofibrillary tangles; SPs – Senile plaques; CAA – Cerebral amyloid angiopathy

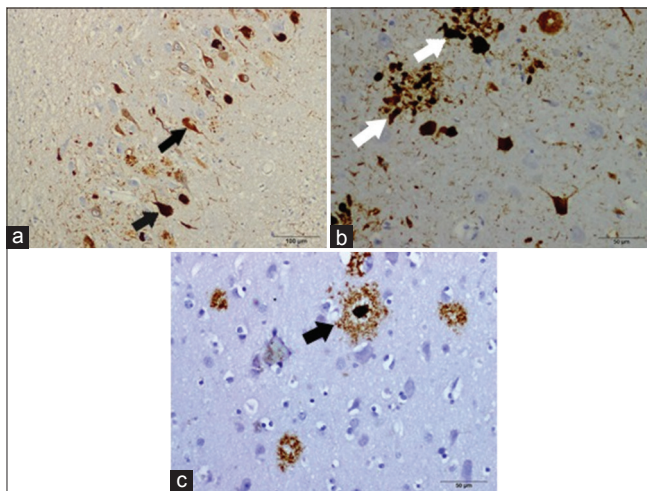


Figure 2: Hall mark lesions of AD. (a) Tau-positive neurofibrillary tangles in hippocampal CA1 region at $\times 10$ (scale bar 100 μm); (b) tau-positive neuritic plaques in hippocampal subiculum region at $\times 20$ (scale bar 50 μm); (c) $\text{A}\beta$ -positive senile plaques in the region of middle temporal cortex at $\times 20$ (scale bar 50 μm)

phosphorylated tau/ubiquitin for CERAD NP score). Further, we have obtained the relative prevalence of comorbid pathologies including CAA, LBDs, IAScW, white matter microscopic infarcts, and WMHs between injury and natural deaths. Thus, apart from AD-related pathologies, other causes of dementia which remain as possible etiological factors in elderly person's injury deaths could be reliably assessed. Moreover, we have employed a vigorous study method to count NFTs and SPs in specific brain regions (hippocampus, entorhinal cortex, superior frontal gyrus, and midbrain); thus, true extent of AD-related pathologies was identified in respect of cause of death.

While this is the first autopsy verification study investigating dementia-related pathologies as etiological factors in injury

deaths, we acknowledge that there are limitations such as sample size, incomplete clinical history of the recruited samples lacking objective psychometry and dementia scores, ubiquitin immunohistochemistry for labeling Lewy bodies instead of α -synuclein, semi-quantitative assessments of certain comorbid pathologies lacking exact quantifications, and nonavailability of some brain regions as specified under minimum tissue requirements by the NIA-AA guidelines. In addition to above restraints, our study was based on cases from suicide and fatal traffic accidents, whereas other causes of injury deaths such as falls and drowning which may result from cognitive impairments also need to be included in future concerns.

Suicide in elderly individuals presents unique challenges to clinicians because older people are less likely to report depressive symptoms.^[28] While high rates of psychiatric symptoms during the course of illness have been reported,^[29] the risk of suicide in people with dementia is generally considered to be low.^[30,31] The contribution of dementia-related pathologies as the cause of suicide in a geriatric population remains questionable. Low risk of suicide in dementia cases has been partly attributed to the higher levels of personal supervision provided in such cases and the difficulties the person with cognitive impairments might have in planning and carrying out suicidal acts. Neuropathological confirmation of AD-related changes in elderly subjects who committed suicide has been limited to few case reports,^[3,4] a single pilot case-control study,^[5] and a large-scale study.^[6] Rubio *et al.*^[5] demonstrated that people with moderate-to-severe AD pathology were over-represented among those who committed suicide, suggesting that presence of Alzheimer pathology may increase the risk of suicide. However, a large scale study by Peisah *et al.*^[6] demonstrated that Alzheimer pathology was not over-represented in elderly suicide victims. The above

studies were limited by the availability of tissue sections, to hippocampal and neocortical examination. Thus, only prevalence of AD-related changes could be reliably assessed. In the absence of AD-related pathology, other causes of dementia such as LBDs or cerebrovascular diseases remain possible risk factors for the etiology in elderly persons' suicidal behavior.

On the other hand, cognitive decline due to aging has received much attention as a possible risk factor for fatal traffic accidents in elderly populations. As dementia becomes a risk factor in traffic accidents, it is reasonable to expect increased dementia-related neuropathologies in the brains of accident victims. However, neuropathological confirmation of AD-related changes in such cases has also been limited with few numbers of studies. The study of Viitanen *et al.*^[7] in the aged motor vehicle drivers highlighted that incipient AD may contribute to fatal crashes of aged drivers. Therefore, the forensic autopsy of these victims should include neuropathological examination. Another similar study done by Gorrie *et al.*^[9] suggested that increased mild neuritic changes, even sparse NPs in the brains of older drivers may be a factor for their cognitive impairments and needs to be replicated elsewhere to clearly establish the association between early AD pathology and crash involvement. Gorrie *et al.*^[8] also carried out a study in older pedestrians and suggested that AD-related pathologies, especially NFTs, are more frequent in fatally injured elders and suggested that cognitive impairment associated with AD; even the earliest stages of AD may be a risk factor for fatal traffic accidents in older pedestrians. In view of above studies, we found that none of the literature cumulatively reported the contribution of dementia, clinically and/or neuropathologically, to the injury deaths in elderly people. Further, none of the above studies assessed the actual burden/true extent of AD-related pathologies among fatal traffic accidents, suicide, and natural deaths. Therefore, despite small sample size, our study would yield a precise estimate of contribution of AD-related pathologies as an etiological factor in injury deaths caused by traffic accidents in elderly people.

There are limited numbers of studies on pathology of AD from India and other low- and middle-income countries (LMICs)^[16,32-42] where the proportion of people affected with dementia is anticipated to rise from 58% in 2010 to 63% in 2030 and 71% in 2050.^[43] Within South Asia, Sri Lanka shows the fastest aging; 13% of population was aged over 60 years in 2011 whereas it was $\leq 8\%$ in rest of the South Asia.^[44] Prevalence of dementia in Sri Lanka based on clinical diagnosis is higher by comparing similar studies of other South Asians reported so far; Sri Lanka - 3.98%,^[45] India - 2.7%,^[46] and Bangladesh - 3.6%.^[47] In Sri Lanka, injury deaths are the second major cause of mortality; 233/100,000 populations in 2008, whereas in other South Asian countries, it is comparatively low (Afghanistan -149; Bangladesh - 91; Bhutan - 105;

India - 99; Maldives - 53; Nepal - 58; Pakistan - 92/100,000 population in 2008).^[44] Among the causes of injury deaths, suicide rate is in peak (34.6 per 100,000 population in 2015) and comparatively higher than in other South Asian populations (Nepal - 7.2; India - 16.0; Bhutan - 12.1; Pakistan - 2.5; Bangladesh - 6.0; Maldives - 11.0; Afghanistan 7.1 per 100,000 population).^[48] Road traffic deaths (road traffic accidents [RTAs]) have also been steadily raising in Sri Lanka and considered as the third leading cause of injury deaths after suicide and collective violence (war-related deaths) and the annual death rate of RTAs is approximately 12.1/100,000 population.^[49] Although death counts due to RTAs are high between the ages of 20 and 55 years, which is likely a result of population age structure, the death rates continue to increase with age and are highest in elderly people.^[49] These are serious public health issues in Sri Lanka as well as in other LMICs; however, it has not been received priority by the government healthcare sectors and it has not been studied extensively by the healthcare professionals. Taken together, our findings suggest that forensic autopsy should include neuropathological examination to the brains of elderly injury deaths caused by fatal accidents aged ≥ 60 years. Further, it is important for primary carers and healthcare professionals 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.

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Conflicts of interest

There are no conflicts of interest.

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