Increased Neurofibrillary Tangles in the Brains of Older Pedestrians Killed in Traffic Accidents

C.A. Gorrie^a M. Rodriguez^c P. Sachdev^{b, d} J. Duflou^c P.M.E. Waite^a

^aNeural Injury Research Unit, School of Medical Sciences, and ^bSchool of Psychiatry, University of New South Wales, ^cDepartment of Forensic Medicine, Central Sydney Laboratory Services, and ^dNeuropsychiatric Institute, Prince of Wales Hospital, Sydney, Australia

Key Words

Alzheimer's disease, autopsy · Pedestrian, elderly · Neurofibrillary tangles · Neuritic plaques

Abstract

Background/Aims: Older people are over-represented in pedestrian fatalities, and it has been suggested that the presence of cognitive impairment or dementia in these individuals may contribute to their accidents. Using neuropathological methods, we aimed to compare the prevalence of dementia pathology in fatally injured older pedestrians with similarly aged ambulatory subjects who died from other causes. **Methods:** The brains of 52 pedestrians (65–93 years) and 52 controls (65–92 years) were assessed for neurofibrillary tangles (NFT), neuritic plaques, Lewy bodies and vascular lesions using established neuropathological criteria. **Results:** The examination for Alzheimer's disease (AD) pathology showed that 43% of the pedestrians had NFT scores of III–VI using Braak and Braak staging, compared with 23% of the controls ($p < 0.05$, Fisher's exact test), indicating incipient, possible or probable AD. There were no differences in the prevalence of pathology for vascular dementia or dementia with Lewy bodies. **Conclusion:** These results suggest that cognitive decline associated with AD, even

in the earliest stages of the disease, may be a factor in fatal traffic accidents for older pedestrians. Special measures for pedestrian safety are necessary in areas with high densities of older citizens and especially for those diagnosed as having a mild cognitive impairment or AD.

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Introduction

People aged ≥ 65 years are over-represented per capita in pedestrian accidents in Australia [1] and other western countries [2]. With the projected increase in the proportion of older people in the population [3] and an expectation that older people will be more active in the future, their safety on our roads is of much concern. Research focused on older motor vehicle drivers has shown an increased risk of accident involvement for those with Alzheimer's disease (AD) [4–7] and that killed drivers have high levels of AD pathology [8]. For older pedestrians cognitive impairment and dementia are often cited as possible contributory factors to traffic accidents [2, 9, 10], but their deaths have not previously been studied systematically for the prevalence of dementia or dementia-related pathology.

Cognitive impairment resulting in dementia affects about 6% of the population >65 years [11]. AD is the most common of the dementia syndromes, followed by vascular dementia (VaD) and dementia with Lewy bodies (DLB). In addition to dementia, mild cognitive impairment (MCI) is thought to affect large numbers of older people and to progress to dementia [12]. While neuropathological findings alone cannot accurately diagnose cognitive impairment, autopsy studies of dementia patients show that specific neuropathological markers correlate with dementia severity when assessed semi-quantitatively [13–17].

If cognitive impairment or dementia are factors in pedestrian accident involvement, it might be expected that the associated neuropathology is more common in fatally injured pedestrians than in people who died from other causes. In this study we assessed the brains of older people who died as a result of a pedestrian accident and the brains of similarly aged controls for neurofibrillary tangles (NFT), neuritic plaques (NP), Lewy bodies and vascular lesions.

Methods

Subjects

The subjects were drawn from people ≥ 65 years who underwent a coronial post-mortem examination at the Department of Forensic Medicine (DoFM), Central Sydney Laboratory Services, between 1997 and 2003. The pedestrian group comprised 52 subjects (24 male, 28 female) who had died following a vehicle-pedestrian accident. The control group consisted of 52 subjects (31 male, 21 female) who had died from another cause, but who had been assessed as being capable of pedestrian activity in the 3 months preceding their death. The control subjects were closely matched to the pedestrians by the age at the time of death. For both groups the subjects were excluded if death was due to a homicide or suicide, if the subject did not fulfil the criteria for organ retention, or if the required brain tissue was not available for examination.

The Human Research Ethics Committee of the University of New South Wales and the Human Ethics Committee of the Central Sydney Area Health Service approved the study. The New South Wales State Coroner granted permission to access the death investigation records.

Neuropathological Assessment

Following fixation in formalin, the brain was examined by a neuropathologist. After a detailed macroscopic examination, which included an evaluation of the blood vessels at the base of the brain, blocks were taken from the superior anterior frontal and superior parietal lobe, the middle and superior temporal gyri, the hippocampus at the level of the lateral geniculate nucleus (including the parahippocampal and fusiform gyri, the entorhinal cortex and usually part of the inferior temporal gyrus) and the midbrain. Serial 6- μ m paraffin sections were stained with haematoxylin and eosin, im-

pregnated with silver (Garvey modified Bielschowsky stain) and immunolabelled with τ - and α -synuclein antibodies.

While blinded as to group, each brain was assessed for the presence of NFT, NP, Lewy bodies and vascular lesions. The NFT were assessed on silver and τ -stained sections using the Braak and Braak (BB) staging method [18], and each case was assigned to 1 of 3 BB groups (0–II, III–IV and V–VI). The NP frequency was recorded from the area of highest density according to the semi-quantitative guide provided by the Consortium to Establish a Registry for AD (CERAD) [19]. The NP frequency was rated as 0, sparse (1–5/mm²), moderate (6–14/mm²) or frequent (>15/mm²). The score of the neocortical region with the highest count was used as the overall score for each subject. The NIA (National Institute on Ageing)-Reagan working party criteria [20], which incorporate both NFT and NP density to give an indication of the likelihood of AD, were also applied, and each case was rated as 0, low or high. For the statistical analysis neuropathological scores were condensed into 2 groups representing those with little or no pathology (normal) and those with moderate to severe pathology (possible cognitive impairment), i.e. NFT (0–II and III–VI), NP (0–sparse and moderate–frequent) and NIA-Reagan scores (0–low and high).

The Lewy bodies were identified in α -synuclein-immunostained sections and scored as densities (per 100 $\times$ field) in the brainstem, hippocampus and neocortical regions based on the criteria of McKeith et al. [21].

The information on the presence of infarcts, lacunes, small vessel disease and atherosclerosis of the major blood vessels in the brain was extracted from the neuropathology report and recorded on a cerebrovascular disease (CVD) form [22]. Cases with infarcts, lacunes, small vessel disease, or those that had a stenosis of >50% in 1 or more of the major cerebral blood vessels, were categorised as having CVD.

Medical Background

The information about the medical history of the subject was extracted from the post-mortem report and the coroner's records. For 10 pedestrian and 5 control subjects, additional information about medical history, activities of daily living, and physical and mental capability was obtained from close family members who participated in a retrospective dementia interview [23]. The completed interviews were blindly rated by a neuropsychiatrist (P.S.) for a clinical dementia rating (CDR) [24] of none (0), questionable dementia/MCI (0.5), mild (1), moderate (2) or severe dementia (3).

Statistical Analysis

Comparisons were made between pedestrian and control samples using χ^2 tests for categorical variables, *t* tests for brain weight (normally distributed) and Mann-Whitney tests for age (skewed towards the younger age groups). Due to the relatively small sample size, Fisher's exact tests were used to compare the data in 2 $\times$ 2 tables. One-sided tests were used to compare those with a normal/mild pathology to those with a more severe pathology, and logistic regression was used to determine the age-adjusted odds ratios (OR) with 95% confidence intervals (CI) for pedestrians and controls with different neuropathological scores. The inter- and intrarater reliabilities for the neuropathological assessment (carried out on 10% of the sample) were satisfactory using Cohen's κ as an index of agreement (κ = 0.75–0.83). Spearman's rank correlation was used to relate the neuropathological assessment to CDRs.

Fig. 1. Graph showing the percentage of pedestrians and controls with high levels of neuropathology for 3 different measures of AD (NFT, NP and NIA-Reagan) and also showing the percentage of pedestrians and controls with a history of dementia, * $p < 0.05$.

Results

Sample Selection

There were 100 autopsies conducted at the DoFM on pedestrians aged ≥ 65 years from 1997 to 2003. Of these 52 met the inclusion criteria for our study. During the same period the admissions of all the people aged ≥ 65 years totalled 8,458. It was not possible or practical to examine the brains of all the non-pedestrian subjects. So 52 that met the inclusion criteria and were closest in age to the pedestrians were selected as control subjects.

Sample Characteristics

The descriptive characteristics for the pedestrian and control groups are shown in table 1. The mean age for men was 77 ± 7.9 years and for women 78 ± 7.1 ($p = 0.42$). The mean brain weight for men was $1,372 \pm 137$ g, which was substantially higher than that for women ($1,207 \text{ g} \pm 114 \text{ g}$, $p < 0.0001$) and did not differ between pedestrians and controls.

The causes of death recorded by the coroner for the pedestrians were multiple injuries (35), head injuries (11), spinal injury (1) or complications following injury (5). For the control group they were heart disease or cardiac arrest (20), multiple injuries (11), head injuries (7), complications following injury (7), a medical condition (5) or undetermined (2).

Neuropathological Findings

Neurofibrillary tangles

The people who died as a result of a pedestrian accident had higher odds of having NFT scores of III–IV than those who died from other causes (adjusted OR = 3.02, 95% CI 1.091–8.353, table 2). Twenty-two pedestrians

Table 1. Descriptive characteristics of the 52 pedestrian and 52 control subjects

	Pedestrians	Controls
Sex (M:F)	24:28	31:21
Age (mean $\pm$ SD), years	77.7 ± 7.3	77.0 ± 7.8
Age range, years	65–93	65–92
Brain weight (mean $\pm$ SD), g	$1,271 \pm 138$	$1,317 \pm 161$

Table 2. Summary of logistic regression for different neuropathological lesions, CVD and clinical history of dementia for pedestrians and controls, adjusted for age

	Adjusted OR	95% CI
NFT (III–VI)	3.02*	1.09–8.35
NP (moderate/frequent)	1.62	0.66–3.99
NIA-Reagan (high)	2.55	0.86–7.59
CVD	0.65	0.27–1.55
Clinical history of dementia	2.48	0.60–10.26

* $p < 0.05$.

(43%) had NFT scores of III–VI compared to 12 controls (12%, $p = 0.029$, Fisher's exact test, fig. 1). There was no significant difference in gender ($p = 0.29$) or mean brain weight ($p = 0.12$) for pedestrians and controls within each NFT group. Those with NFT scores of 0–II were significantly younger than the III–VI group ($p < 0.0001$), but there was no difference in the mean age of pedestrians and controls within each NFT group.

Neuritic Plaques

As shown in figure 1, more pedestrians (31%) had moderate/frequent NP densities than controls (23%), but these differences were not statistically significant ($p = 0.18$, Fisher's exact test). The assessment by the NIA-Reagan criteria, incorporating both NFT and NP, indicated that 13 pedestrians (25%) had a high likelihood of AD compared to 6 controls (13%, $p = 0.06$, Fisher's exact test). The age-adjusted OR for different neuropathological lesions are shown in table 2.

Cerebrovascular Disease

Thirty-four (65%) pedestrians and 38 (73%) controls showed some form of CVD including small vessel disease, infarcts, lacunes or atherosclerosis. There was no significant difference in the frequency of each of these lesions for pedestrians and controls using χ^2 tests ($\chi^2 = 3.5$, degrees of freedom 3, $p = 0.32$). Five of these pedestrians and 4 of these controls also had a mild, moderate or severe stenosis of at least 1 of the internal carotid arteries but with no apparent difference between the groups. Only 2 of these subjects (1 pedestrian and 1 control) had severe CVD and a history of dementia. One of these subjects was diagnosed as having mixed VaD and AD, while the other had mixed VaD, AD and frontotemporal dementia.

Lewy Bodies

Cortical Lewy bodies were not identified in any pedestrian or control brains. Two controls and 1 pedestrian had a history of Parkinson's disease. Idiopathic Parkinson's disease (brainstem Lewy body disease) was confirmed in 1 case. In the other 2 cases no lesions likely to result in parkinsonism were identified. Preclinical brainstem Lewy body disease was identified in another 3 subjects (1 pedestrian, 2 controls) with rare Lewy bodies in the dorso-lateral substantia nigra without significant cell loss. A review of the clinical information available did not suggest a clinical diagnosis of DLB for any of these cases.

History of Dementia

Although no rigorous clinical evaluation of dementia could be made in this sample, the review of the death investigation reports identified 7 pedestrians (14%) and 3 controls (5.6%) with a history of dementia (fig. 1, $p = 0.16$, Fisher's exact test). They all fulfilled the CERAD diagnostic criteria for possible, probable or definite AD, and 7 out of 10 had NFT scores of III–VI. Of these 7 cases 1 also had progressive supranuclear palsy. Of the 3 cases with NFT scores of 0–II, 1 had mixed frontotemporal dementia and VaD, 1 had VaD, and the third had mod-

erate small vessel disease and lacunes. Of the 10 subjects with a history of dementia, 5 had a high or intermediate likelihood of dementia being caused by AD, using the NIA-Reagan rating. Three subjects with a low-intermediate NIA-Reagan rating also had progressive supranuclear palsy, frontotemporal dementia/VaD and VaD. The remaining 2 subjects had a low and a low-intermediate NIA-Reagan rating and no other pathology to explain their dementia.

Retrospective Dementia Interview

A small subset of subjects (10 pedestrians and 5 controls: 14.4%) was further assessed using a previously validated retrospective dementia interview with a close collateral source. The CDR ranged from 0 to 2 for these subjects and positively correlated with the NFT scores (resolution = 0.62, $p = 0.02$) and NP density (resolution = 0.51, $p = 0.04$) using Spearman's rank correlations. An overview of the physical health of these subjects showed that they were all physically capable of performing personal care functions for themselves, and 80% of both the pedestrians and controls were reported as having no mobility problems. The remaining 20% were still active but described as having a limited walking ability, especially uphill or when climbing steps. These people usually avoided routes that they found problematic. The medical conditions of these 15 pedestrians and controls were diverse, but there were no differences between the 2 groups for the 10 medical conditions that were identified ($\chi^2 = 4.1$, degrees of freedom 9, $p = 0.9$).

Discussion

This study found that pathological lesions associated with AD, especially NFT, are more frequent in the brains of fatally injured elderly pedestrians than in similarly aged controls. This suggests that the cognitive impairment associated with these lesions may be a risk factor for pedestrian accidents in the elderly.

Braak and Braak [18, 25] described a topographical staging system for AD-related pathology with a 6-stage hierarchical progression of NFT accumulation, initially involving the transentorhinal and entorhinal cortex (stages I–II), followed by the hippocampus and other limbic regions (stages III–IV) and finally involving the neocortex (stages V–VI). Subsequently a number of groups have prospectively investigated cohorts of aging people and found positive correlations between the BB stage at autopsy and the severity of dementia as tested on a range of

psychological measures [13–17, 26]. We used BB stage III in our study as the threshold for the cognitive decline. While not an absolute measure, the earliest changes in cognition appear to be associated with a distribution of NFT into the limbic structures and would equate to a BB stage of $\geq$ III [17, 18]. This is particularly thought to be the case in the older age groups [27]. One study [17] found that the memory performance decreased between stages II and III, and the mental status declined after stage III. The subtle decline in memory and executive function in a group of cognitively intact elderly subjects (CDR = 0) was associated with a neuropathological diagnosis of normal or possible AD (CERAD criteria) and BB stages II or III [13].

There were slightly more female than male pedestrians in our sample (53.8%), especially in the group with high (III and VI) NFT scores (59%). It has recently been reported that women have a higher risk of both NFT and plaque pathology than men at a given age [28], but previous research found the prevalence of neuropathological lesions to be independent of gender [29]. In our study there were no statistical differences in either the number or the age of male and female pedestrians and controls in different NFT groups, indicating that the women in this sample did not have more severe neuropathology than men of the same age. The age-related increases in NFT pathology seen in our sample are consistent with that reported by Braak and Braak [25].

A proportion of all older people will have some degree of neurofibrillary pathology, and 23% of our control group had NFT scores of III and VI. This is within the range reported by others in cognitively normal cohorts of older people and in large unselected autopsy studies [13, 18, 25, 30–32].

While there is a positive correlation between NP frequency and AD [13–17, 25], the relationship has been reported to be less strong than that for NFT [16, 17]. In cognitively normal people or those with an MCI, the significance of NP is less clear, with some studies finding no NP in the brains of cognitively normal subjects [30], others reporting moderate numbers of NP in 5% of cognitively normal subjects [13], and 1 study finding an NP pathology which ‘met the CERAD criteria for AD’ in up to 25% of cognitively normal subjects [30]. It has also been suggested that in MCI and mild AD (CDR = 0.5–1) diffuse plaques may predominate in the neocortex with a shift to a higher proportion of NP later in the progression of AD [33]. In our study, following the CERAD guidelines, only neocortical NP were assessed, and although the densities were higher in pedestrians compared to the con-

trols, this was not a significant difference. These results may reflect the variability of the NP pathology in those with no or MCI compared to those with a more severe disease, or they may indicate that, in contrast to NFT, the NP frequency is not strongly associated with cognitive decline affecting unsafe pedestrian behaviour.

In a neuropathological investigation of older killed Swedish drivers by Viitanen et al. [8] nearly half (47%) of the subjects were found to have high levels of NP pathology. Our findings indicated that 31% of the pedestrians and 23% of the controls had moderate or frequent NP. Comparing the 2 studies is difficult, as pedestrians may differ from drivers in their demographic make-up, there may be geographical differences between the 2 countries, or the methodologies may vary. Even without any control group for comparison, 47% of killed drivers with NP pathology is high and implies that incipient AD may have contributed to the fatal crashes of these aged drivers.

The CVD rate was found to be similarly high for pedestrians (65%) and controls (73%) in this sample group. It should be noted, however, that only a relatively small amount of white matter tissue was examined as part of the neuropathological examination, and with an increased interest in the role of CVD in AD, a more detailed white matter analysis may be useful in future studies. The frequency of VaD (1.9%) seen in our sample was comparable to that previously reported in community-dwelling elderly people [34]. The absence of DLB in our subjects reflects the low prevalence of DLB in people $\geq$ 65 years (0.1%) [35]. In addition to meeting the CERAD criteria for possible or probable AD, 2 pedestrians had pathological evidence of mixed dementia (VaD and frontotemporal dementia) or progressive supranuclear palsy. These conditions are uncommon, causing up to 5.4% of dementia, and are rarely identified in population-based studies [36, 37]. Their presence in 2 pedestrians in a comparatively small study further suggests that cognitive decline is an important factor in pedestrian accidents.

Observational studies of pedestrian behaviour suggest a poorer performance in the elderly, especially when the road environment is complex. Compared to younger pedestrians, older people take longer to step off the kerb, leave smaller safety margins and are less likely to wait until the entire road is clear before starting to cross [9]. Similarly, in more controlled off-road experiments, older people tend to make less safe judgements about whether to cross the road, particularly when they are given a shorter time in which to make the decision [38]. Several publications refer to declines in reaction time, information processing, attention capability and decision-making as

possible factors in older pedestrians' accidents [2, 9, 10, 38].

By studying the most severe pedestrian accidents, those resulting in death, we have investigated whether a higher frequency of lesions associated with cognitive impairment in this group, compared with similarly aged controls, might contribute to poor decision-making and hence poorer road safety performance. Although the cognitive function cannot be directly assessed post-mortem, many studies have indicated that relationships exist between some types of neuropathology and cognitive impairment as discussed above. Older people with increased NFT and NP burdens may have an undiagnosed MCI. These people may engage in pedestrian activity unaware that their cognitive ability is compromised and that this could affect their safety in the road environment.

In addition, a history of dementia was over-represented in our sample of fatally injured elderly pedestrians (14%) compared to the control group (5.7%) and when compared to older population samples (6%) [11]. The cognitive decline in these people was severe enough for a clinical diagnosis of dementia and was likely to have impaired the daily function. Particular emphasis on safe pedestrian behaviour for people with diagnosed cognitive impairment is recommended.

While the focus of our research has been on the examination of dementia pathology, we cannot discount other medical or physical conditions affecting these older subjects. Declines in vision, hearing and mobility are common in the elderly, and while there is little empirical evidence directly linking these conditions to pedestrian accidents, most road safety countermeasures for older pedestrians are aimed at addressing the deteriorating functional ability of older people [2, 39]. While we could not control for medical or physical conditions in this current autopsy study, we were able to ascertain, from collateral interviews, that a subset of both pedestrians and controls had similar types of coexisting medical conditions. This indicates that no single condition was more frequent in the pedestrian group, and that the physical limitations for walking were likely to be similar for both groups.

There are some limitations in this study that should be noted. Firstly, all the subjects were recruited from the DoFM. Coronal investigation of traumatic deaths is mandatory in New South Wales, Australia, whereas only a small proportion of non-traumatic deaths are referred to the coroner, and so our control group is not a random sample of all deaths in the community. It could be argued that our control sample is biased toward certain conditions that necessitate a post-mortem examination. Al-

though difficult to evaluate, it does not appear that deaths associated with neurological conditions resulting in cognitive decline were preferentially referred or not referred to the coroner. Secondly, the amount of pre-mortem information available for each individual varied greatly. Although data about medical, cognitive or physical conditions relevant to the circumstances surrounding the death were available from the death investigation reports, there was no rigorous or uniform clinical evaluation of dementia. While great care was taken to evaluate all the available sources of information, it is possible that cognitive decline was not identified in some subjects.

Conclusions

Our results show that AD pathology, particularly NFT, is increased in the brains of older people who were fatally injured in pedestrian-vehicle accidents. This may indicate that MCI and preclinical AD, as well as overt dementia are risk factors for fatal accidents in older pedestrians. This has implications for clinicians in the early detection of cognitive impairment in the elderly and for road safety advisors in developing strategies for older pedestrians with cognitive impairment.

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