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Continued Overleaf

Alzheimer's disease—time to act is now

It is not too late to start a national programme to tackle the disease

Increase in life span is correlated with increase in dementia. Dementia is an acquired impairment in our intellectual abilities; it affects memory, language, visuospatial skills, cognition, emotion and personality. As we age, we all experience memory deficits—we do not remember where we put items, we forget appointments, and we temporarily forget names of individuals we know and names of places we have recently visited. To forget where we have put our keys is a memory deficit, but to forget what a key is used for is dementia.

What can be more frightening to individuals as they age than the thought of becoming demented in the near future? To many, the thought of becoming mentally incompetent is more frightening than the thought of a physical ailment. To be dependent on others for all our needs, to be incapable of expressing our feelings, to be unable to recognise our families, and to lose our ability to reason is utterly demoralising for any individual. As we age, we all slow down. Our recall time increases, as does our forgetfulness. In dementia, though the basic wiring system in the brain remains intact, the wires are cut. We are unable to reason, our memories fail, and we cannot function well. We have lost the essence of being that makes us persons. At the end, there is no person but only a living creature.

Alzheimer's disease (AD), which accounts for 65–70% of all cases of dementia, is an irreversible progressive dementia of long duration. The disease is characterised by difficulty in learning and retaining new information, with increasing problems that affect calculation, visuospatial skills, performance of purposeful acts, and language. The four hallmarks of AD are amnesia, apraxia, agnosia and aphasia. Risk factors for AD include aging, family history, cardiovascular disease, high blood levels of cholesterol and homocysteine, presence of e4 allele of the apolipoprotein gene (apoE4), and in a small number of patients with early-onset AD, genetic inheritance from mutations of chromosomes 1, 14 and 21. Protective factors include higher education, challenging occupation, and the presence of one or both apoE2 alleles. The neuropathological hallmarks in the brain are neuritic plaques, neurofibrillary tangles and neuronal degeneration particularly in the cholinergic pathways [1]. At present, AD is diagnosed on the basis of the development of multiple cognitive deficits and significant impairment of social and occupational functioning, with gradual onset, continuing decline and lack of alternative explanations (e.g. delirium, other central nervous system and psychiatric conditions, systemic diseases) [2]. In the absence of a proven diagnostic marker, the diagnosis of AD remains based on the clinical judgement that the patient's cognitive function has declined significantly from past levels of ability. An accurate history of the onset and course of the

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disorder, usually obtained from an informant who knows the patient well, and direct cognitive testing are essential for the diagnostic process. Other investigations including routine blood biochemistry and radiological imaging of the brain, particularly assessment of medial temporal lobe thickness, improve the diagnostic accuracy of the disease [1]. Recent clinicopathological studies have recorded a diagnostic accuracy exceeding 90% when established criteria are used [1].

In AD the progressive decline in cognitive function is associated with a decrease in the patient's ability to perform daily activities such as managing money, moving around, cooking, feeding and bathing [3]. The neuropsychiatric symptoms (NPS) of AD, also referred to as behavioural and psychological symptoms of dementia, occur throughout the course of the illness and include psychotic symptoms, mood alterations, agitation and apathy [3]. As a result of patients' loss of autonomy with increased functional disability and emergence of NPS, caregivers experience the burden of progressively increasing daily care required by the patient, which leads to social isolation, financial hardship and a variety of emotional stresses, such as depression and anxiety [4].

The incidence and prevalence of AD increase exponentially with age, and it is estimated to affect up to 4–8% of people over the age of 65 years and nearly half of people aged 85 years and above in Europe and the United States [5]. Currently, more than 3 million persons in Europe and about 4 million in the US are estimated to be suffering from dementia, and approximately 800,000 new cases will be diagnosed every year in Europe alone [6]. The average yearly cost of care per person is more than US\$ 35,000, with estimates of the total cost varying from US\$ 60 billion to US\$ 200 billion annually in the US [6].

A few studies from India have reported low total and age-specific prevalence rates of dementia [7, 8] suggesting that dementia in general and AD in particular are uncommon in South Asia. However, we recently reported a dementia prevalence of 4% from a regional community survey of people over 65 years in Sri Lanka, and more than 70% of these were of the Alzheimer type [9]. This is the highest reported dementia prevalence in the region, and is similar to prevalence rates in the West. These findings assume importance in the context of Sri Lanka's rapidly aging population, which would constitute about one fifth of the entire population in the next 15–20 years. If this predicted demographic shift does not change, we estimate that more than 200,000 Sri Lankans over 65 years will be suffering from AD by 2020.

Numerous approaches have been explored to treat individuals with AD. However, the inhibition of cholinesterase (ChE), the enzyme responsible for acetylcholine (ACh) catabolism, is the most extensively studied and best developed therapeutic approach for the treatment of AD. It provides benefit presumably through an increase in synaptic ACh levels and enhanced cholinergic neurotransmission. The National Institute for Clinical Excellence (NICE) in the UK [10], and the American Academy of Neurology [11] recommend that therapy with ChE inhibitors should be given to all AD patients with mild-moderate symptoms. Four ChE inhibitors, tacrine hydrochloride, donepezil, rivastigmine and galantamine have been approved for the symptomatic treatment of patients with AD. Although it is currently not available through our National Health Service, rivastigmine is registered for use in Sri Lanka [12]. Approximately 40–50% of patients exposed to these agents show significant improvement in the core symptoms of AD such as memory, orientation and concentration. Furthermore, these agents also improve global functioning (or ADL) [13] and reduce NPS in AD [14], which has a profound effect on the patient's quality of life and the caregiver's stress burden [13]. A recent meta-analysis showed that the number of patients who needed treatment with a ChE inhibitor compared with placebo for one additional patient to demonstrate a global response (NNT) was 12 [15]. In

contrast, the reported NNT for antihypertensives to prevent one major event varies between 29 and 86 [16]. However, response to treatment with ChE inhibitors may be influenced by timing and genetic make up. Substantial evidence suggests that patients with AD in the mild-moderate stage have a stronger response to ChE inhibitor therapy than do patients with AD in the severe stage [17], and patients with one or both alleles of apoE4 respond poorly to the therapy [15]. To date one of the largest treatment effects to ChE inhibitors have been reported from a Japanese population of AD patients [15]. Although no definite conclusion can be reached on the basis of a single study, the low frequency of apoE4 genotype in the Japanese [15] may explain this finding. Interestingly, the reported apoE4 allele frequency in Sri Lankans [18] is similar to that reported from Japan, suggesting that a similarly large treatment response to ChE inhibitors may be seen in our AD patients.

AD is uncommon before the age of 65 years. However, after 65, the prevalence doubles approximately every 5 years. Given that the disease prevalence doubles every 5 years, delaying the onset of appearance of the disease by 5 years would result in a 50% reduction in prevalence in one generation. Delaying onset by 10 years would again halve the prevalence, reducing it by 75%. Thus delaying the onset of disease or even slowing the progression of AD in the early stages, if possible, would yield enormous medical, social and economic benefits. Recent epidemiological studies with different study designs and patient populations have shown a 40–70% reduction in the risk of AD associated with the use of cholesterol lowering agents, statins [19]. Similar benefits have been reported with high dose vitamin E. The American Academy of Neurology now recommends 1000 IU of vitamin E twice daily as a standard care for the treatment of patients with AD, particularly in the early stages of the disease [15].

AD, as the loss of mind, potentially threatens the very essence of what it is to be human. As the number of elderly persons continues to increase dramatically over the next decade, the magnitude and complexity of the problems associated with AD will continue to grow, and this devastating disease will become a major public health problem in our country. In the absence of formal care services in Sri Lanka there is a heavy reliance on informal, in particular family care for patients with AD. Therefore, understanding the scale of the problem is important for motivating the Government, industry, and professional bodies to rise to the challenge of AD. The solution of the problem of AD will require an attack on multiple fronts designed to reduce numbers of individuals affected, the duration of disability and the burden on families and carers. This will require making specific drug therapy accessible to all patients, developing support and care programmes for patients to enable family caregivers to bear the burden of care, and more research, particularly in pharmacoconomics of the disease relevant to Sri Lanka.

The complexity of the problems of AD, and the enormous burden it imposes speaks for the urgency of developing a national programme to face this dilemma. There is much to be done, and Sri Lanka will do well to at least start now. In the meantime, patients and their physicians should be instructed that the incidence and morbidity of AD may be reduced by appropriate lifestyle changes to minimise risk factors, and by early detection and aggressive treatment of the disease.

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Adverse effects of pethidine

Norpethidine is the active metabolite of pethidine. It accumulates in both the mother and fetus with a half-life of 20.5 hours and is thought to be responsible for adverse neonatal effects including respiratory depression. Newborns exposed to pethidine have significantly impaired normal infant behaviours such as hand and mouth movements, nipple touching before suckling, and licking movements. Half of the infants exposed to pethidine fail to breastfeed and cry more in the neonatal period. In addition to the maternal sedating effects of pethidine, there is also the theoretical risk of maternal delayed gastric emptying, aspiration and respiratory depression. Norpethidine can also induce seizures.

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