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Dementia: Update on causes and prevention, including the role of COVID-19

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Dementia is steadily increasing worldwide with major individual, family, societal, and economic consequences. This long-read blog details how, although treatment is currently largely ineffective and aspects of the underlying pathophysiology unclear, there is good evidence that much of it is preventable. In particular measures overlap with those for: preventing cardiovascular disease and diabetes (e.g., diet, physical activity, control of obesity); preventing head

injuries (e.g., from falls and traffic injuries); advancing alcohol control; and, it is becoming increasingly clear, preventing respiratory infections (e.g., vaccination against influenza and COVID-19).

Introduction

We live at a time when more of us are living into old age than at any other period of human history. This is accompanied by an increasing burden – on individuals, whānau, and the healthcare system – of neurodegenerative disorders, again in proportions not previously experienced by human populations. There is a tendency to regard neurodegenerative disease, and especially its manifestation as dementia, as an inevitable consequence of ageing. However, as with all disorders, dementia has causes, some of which are identifiable and potentially preventable.

Dementia is a progressive syndrome, characterised by deteriorating cognitive function, involving memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. This impairment is commonly accompanied by changes in mood, emotional control, and behaviour [1]. It is a consequence of a variety of brain disorders and injury and one of the major causes of disability among older people. Worldwide prevalence exceeds 55 million people; there are almost 10 million new cases annually; and it is the seventh leading cause of death among all diseases [1].

The best known form of dementia – Alzheimer's – was first described (both clinical presentation and microscopic pathology) at a meeting of psychiatrists (then known as alienists) in Tubingen, Germany in 1906 and subsequently published in 1907 [2]. The paper is seldom cited but there is an English translation available [3].

Dementia can manifest differently in different people but is generally described as developing in three stages [1]. The first can be missed and is characterised by: impairment of memory; losing track of time; and becoming lost in familiar places. Subsequently, memory deteriorates further with forgetfulness of names and recent events; becoming confused at home; losing communication skills and personal-care habits; repeated questioning; and wandering. Finally, there is increased difficulty walking, progressing to inactivity and almost total dependence; memory loss is marked, involving failure to recognise relatives and friends and being disoriented in time and place; changes in behaviour can be prominent, including marked lack of personal care and the emergence of aggression.

Although dementia is often classified on the basis of pathology and syndromic features – particularly as Alzheimer's disease (accounting for 60-70% of cases), vascular dementia, dementia with Lewy bodies (protein aggregations in nerve cells), and frontotemporal dementia – the reality is that the boundaries among these are poorly demarcated and "mixed forms often co-exist" [1]. For instance, Alzheimer's and vascular dementia are thought to be distinguishable (Alzheimer's is a disorder of neurons rather than blood vessels) and do show differences in pathology. However, there is a degree of overlap in their manifestations [4,5] and they share some pathologic changes in neuronal scaffolding proteins, suggesting, perhaps, that cerebral atherosclerosis contributes to the development of Alzheimer's [6].

There are no cures for dementia and, although some pharmaceuticals have been developed particularly for Alzheimer's, there are no resounding treatment successes to date. Management involves support for patients and their carers (who are most frequently family

and whānau) in order to optimise physical activity, stimulate cognition and memory, and treat any accompanying physical or mental illness. It is important to remember that dementia has a disproportionate impact on women: they account for 65% of deaths due to dementia; disability-adjusted life years (DALYs) due to dementia are approximately 60% higher in women than in men; and women provide 70% of informal carer hours [1]. Age is the most important risk factor for dementia but it is not confined to older people – young onset dementia (defined as the onset of symptoms before the age of 65 years) accounts for up to 9% of cases [1]. In 2019, the estimated total global cost of dementia was US$ 1.3 trillion [1] with costs expected to rise as both numbers and cost of care increase.

As a result of very recent scientific sleuthing, it appears that we may know less about the pathobiology of dementia than we imagined: at least some aspects of what were thought to be key data on Alzheimer's disease are under close scrutiny for possible inappropriate manipulation [7]. However, conversely, we know more about possible causes and, therefore, about prevention than we often seem to recognise. There are at least five clusters of causes.

Adverse neurological sequelae of cardiovascular disorders

Stroke is the second leading cause of death and a major cause of disability worldwide. Both modifiable and non-modifiable risk factors can affect the occurrence. Among these, atherosclerosis is well-recognised as a major contributor to the rising incidence of stroke-related mortality and morbidity. A meta-analysis involving 7511 individuals in 22 hospital-based and eight population-based cohorts was undertaken to assess heterogeneity in the reported rates of pre-stroke and post-stroke dementia and to identify risk factors. The researchers found that: 14% of hospital-based patients and 9.1% of population-based individuals had dementia before their first stroke; approximately 10% developed newly diagnosed dementia soon after their first stroke; and more than a 40% developed dementia after a recurrent stroke. Most of the predictors of post-stroke dementia were either directly related to stroke or potentially related to recurrent stroke or the presence of several lesions. The researchers noted that the strong association between multiple strokes and post-stroke dementia and the prognostic value of other stroke characteristics "highlight the central causal role of stroke itself as opposed to the underlying vascular risk factors" [8].

A more recent systematic review was undertaken to explore the relationships between blood lipids, atherosclerosis, and statin use on the one hand and dementia and cognitive impairment on the other with the goal of synthesising the evidence among stroke patients. A total of almost 40,000 stroke patients from one randomised controlled trial (RCT) and 55 cohort studies were studied. The pooled odds ratios (ORs) for dementia and cognitive impairment among those with coronary heart disease were 1.3 and 1.2 respectively. The corresponding ORs for peripheral artery disease were 3.6 and 2.7 and, for carotid stenosis, 2.7 and 3.3. For post-stroke statin use, the corresponding ORs were 0.89 and 0.56 respectively. There was no association with high cholesterol levels (hypercholesterolemia). These data – both the increased risk of cognitive impairment and dementia among stroke patients associated with a variety of vascular conditions and the reduced risk of cognitive impairment associated with statin use – implicate atherosclerosis directly [9].

Diabetes and dementia

Steadily accumulating evidence shows an association between type 2 diabetes and dementia. Meta-analyses show an increased risk of dementia of all types as well as

specifically Alzheimer's and vascular dementia [10,11]. Individuals with diabetes have been shown to have a reduced glycolytic flux in the brain [12]; the authors argue that generally impaired brain glucose metabolism may be intrinsic to Alzheimer's disease but whether the abnormal glucose metabolism is a cause, a correlate, or a consequence of dementia remains to be clarified. There is trial evidence that dietary management of diabetes (via a ketogenic diet) improves some biomarkers of Alzheimer's but memory test results did not differ between those on the ketogenic diet and those on the American Heart Association Diet [13]. An observational cohort shows that those with untreated diabetes progress to dementia at a faster rate than those who with normal blood glucose [14]. There are also twin-study data to show that overweight and obesity (without reference to diabetes) is a risk factor for dementia [15]. The overall tentative conclusion that can be drawn from these data at the moment is that diabetes is a precursor or a risk factor for dementia and that control of diabetes may reduce that risk.

Trauma-related neurological outcomes

Mild traumatic brain injury (TBI) is a common occurrence in contact sports, such as rugby and boxing. TBI is defined as non-penetrating injury resulting from blunt trauma. There is no specific imaging or biomarker test for mild TBI [16].

Large national cohort studies in Taiwan [17], Sweden [18], and Denmark [19], involving a total of more than 6 million patients have shown an elevated risk of dementia following a history of even a single mild TBI, with statistically significant hazard ratios (HRs) ranging from 1.3 to 3.8. The association was stronger among those with more severe and multiple trauma but was seen even 30 years after the original injury [18]. The Taiwanese study was able to control for age, sex, urbanization level, socioeconomic status, diabetes, hypertension, coronary artery disease, hyperlipidaemia, history of alcohol intoxication, history of ischemic stroke, history of intracranial haemorrhage, and comorbidities and reported an adjusted HR of 3.3 (95% confidence interval [CI]: 2.7–3.9) [17].

A smaller study of patients within a California state-wide administrative health database of emergency department and inpatient visits reported that moderate to severe TBI at ≥55 years and mild TBI at ≥65 years had an elevated risk of developing dementia compared with those with non-brain trauma [20].

A cohort study within the US Veterans Health Administration health care system involved more than 350,000 patients with and without TBI [21]. A total of 10,835 (6.1%) with TBI developed dementia compared with 4,698 (2.6%) without TBI. After adjustment for demographics and medical and psychiatric comorbidities, adjusted HRs for dementia were 2.4 (2.1-2.7) for mild TBI without loss of consciousness (LoC), 2.5 (2.3-2.8) for mild TBI with LoC, 3.2 (3.1-3.3) for mild TBI with LoC status unknown, and 3.8 (3.6-3.9) for moderate to severe TBI.

Alcohol-related dementia

A subset of the UK Whitehall II observational cohort underwent weekly measures of alcohol intake, repeated measures of cognitive performance between 1985 and 2015, and multimodal magnetic resonance imaging (MRI) at study endpoint. The sub-cohort included 550 men and women (mean age 43 at baseline), none of whom was alcohol dependent by CAGE (mnemonic acronym for the widely used short screening alcoholism questionnaire) [22] criteria. Higher alcohol consumption over the 30-years of follow-up was associated with increased odds of atrophy to a specific region of the brain (the hippocampus) in a dose-

dependent fashion, as well as impaired white-matter microstructure [23]. Hippocampal atrophy has also been shown to distinguish patients with Alzheimer's disease from those with mild cognitive impairment (MCI) and people who are cognitively normal [24]. The highest risk in the Whitehall II sub-cohort was seen in people consuming over 30 drinks a week: compared with abstainers, odds ratio (OR) = 5.8, 95% CI: 1.8-18.6; p<0.001). For those drinking 14-21 drinks/week, OR = 3.4 (95% CI: 1.4-8.1; p = 0.007). There was no evidence to suggest that light drinkers (1 to <7 drinks/week) were protected from cognitive decline compared with non-drinkers. Higher alcohol use was also associated with differences in corpus callosum microstructure and faster decline in lexical fluency.

In Denmark, 19,002 alcohol-dependent individuals were compared with 186,767 controls from the general population. Alcohol-dependent men and women had statistically significantly higher risks of well-established alcohol-related diseases (and deaths from those diseases) and for dementia (men: HR = 2.0; 95% CI: 1.6–2.3; women: HR = 2.4; 1.8–3.2) [25].

Adverse neurological sequelae from respiratory infections

Most recently, it has become clear that infections – particularly viral infections – are centrally involved in insults to the brain and subsequent neurodegeneration. Danish researchers used electronic health records – covering about half the population – to investigate people who had been tested for COVID-19, diagnosed with community-acquired bacterial pneumonia, or tested for influenza over the same period during the COVID pandemic. More than 900,000 people were tested for COVID-19, of whom 43,375 tested positive. COVID-19-positive outpatients had a higher risk of Alzheimer's (RR = 3.5) and Parkinson's disease (RR = 2.6) as well as both ischaemic and haemorrhagic stroke than those who tested negative. Frequencies of other neurologic diseases including multiple sclerosis and Guillain-Barré syndrome did not differ among the groups [26]. The researchers seemed to forget their own study design and concluded: "…reassuringly, most neurological disorders do not appear to be more frequent after COVID-19 than after influenza or community-acquired bacterial pneumonia." Why this is reassuring escapes me as a more plausible interpretation is that respiratory infection can be a risk factor for (or at least a trigger of) neurodegenerative disease. There are some modest hints elsewhere that Parkinsonism may be a sequela of influenza, perhaps in an influenza strain-specific manner [27].

A study of records from a large US claims database – with data spanning September 1, 2009 through August 31, 2019 – is consistent with this broader interpretation of the impact of respiratory disease. Eligible patients were free of dementia during the 6-year look-back period and ≥65 years old at the start of follow-up. Propensity-score matching on demographics, medication usage, and comorbidities allowed the creation of influenza-vaccinated and influenza-unvaccinated cohorts, resulting in 935,887 matched pairs. The subsequent risk of Alzheimer's was markedly lower (RR = 0.60) in those who had been vaccinated against influenza [28].

Taquet and colleagues undertook a 2-year retrospective cohort study of neurologic and psychiatric consequences of COVID-19 [29]. They studied almost 1.5 million patients, matched with an equal number of patients with another respiratory infection, using de-identified data from the TriNetX electronic health records network, encompassing records of approximately 89 million patients mostly from the USA. They reported that risks of common psychiatric disorders returned to baseline after 1–2 months. In contrast, risks of cognitive deficit (known as "brain fog"), dementia, psychotic disorders, and epilepsy/seizures were

still higher in those diagnosed with COVID-19 than among the control group at the end of the 2-year follow-up period [29].

Evidence for direct damage to the brain by viral infection comes from several different studies of SARS-CoV-2 (the virus that causes COVID-19):

First, brain fog, a post-acute-infection phenomenon that resembles cancer-therapy-induced "chemo-brain" is a common symptom of long COVID [30,31]. Second, a variety of other psychologic and neurologic symptoms and signs are common in long COVID [32-34]. Third, in a study that took advantage of the fact that participants in the UK Biobank had undergone multimodal brain imaging, 785 participants were imaged twice: 401 cases who tested positive for SARS-CoV-2 between scans (an average of 141 days separated COVID diagnosis and second scan) and 384 controls. This pre/post sequential scanning ensured interpretable relationships across time. Statistically significant longitudinal effects in the COVID-19-affected group included: a) greater reduction in grey matter thickness and changes in contrast-medium diffusion as a proxy for tissue damage; b) greater evidence of tissue damage in regions functionally connected to the primary olfactory cortex (consistent with the common loss of sense of smell with COVID-19); and c) greater reduction in overall brain size. The researchers hypothesised that the brain damage may result from: a spread of the disease via olfactory pathways; neuroinflammatory events; or the loss of sensory input due to loss of sense of smell. The infected participants also showed a larger cognitive decline between time points [35]. Fourth, three different approaches have demonstrated that SARS-CoV-2 can invade brain tissue [36].

Pathologic mechanisms, especially the role of inflammation

Although some of the accepted pathology of Alzheimer's is now seen as problematic [7], the role of immune cells and inflammation has moved more to centre stage. Microglia are macrophage-like immune cells with normal roles in central nervous system development and homeostasis; they account for 5-10% of brain mass [37]. They sculpt developing neural circuits by eliminating some neurons and "pruning" axons and synapses [38]. Later in development and into adulthood, microglia processes are highly motile and continually survey their local environment [39], scanning the entire volume of the brain over the course of a few hours [40]. They normally reside throughout the central nervous system and act as sensors of pathologic events, becoming activated just in areas of damage or loss of function [41]. Such inflammatory activation is a feature of cancer-therapy-induced cognitive impairment [42]. Genetic research (including genome-wide association studies) and systems approaches have identified microglial genes and networks that are implicated in Alzheimer's [37,43-46]. Inflammation has been shown to be central to the pathology of Alzheimer's [47] and inhibition of inflammatory responses in a mouse model resulted in fewer plaques and reduced microglial activity [48].

As a result of the recent pandemic, some other important insights into the pathology of dementia and the role of infection have emerged as researchers have sought to understand the mechanisms that produce COVID-related brain fog. Both SARS-CoV-2 and the H1N1 subtype of influenza A produce relevant neurologic damage in mice and the pathway involves a particular chemokine ligand called Eotaxin-149, which has also been associated with age of onset of Alzheimer's disease [50].

Prevention of dementia

In the absence of cure and even particularly effective treatment, prevention must be a

primary consideration [51-53].

Whatever the exact relationship is, it is clear that some forms of dementia are embedded deep in the cluster of cardiovascular pathophysiologic events that include atherosclerosis, hypertension, and stroke. Therefore, it is likely that the most useful approach to primary prevention of atherosclerotic dementia and perhaps some other forms as well, involves healthier diets (ie, more focus on plant-based diets that are low in salt and low in saturated fats), physical activity, and weight control. Secondary prevention would include pharmaceutical approaches to hyperlipidaemia (e.g., statins) and hypertension (anti-hypertensive medicines). A similar approach to prevention and management of diabetes would reduce its impact on dementia.

Alcohol consumption is a major problem globally. We have allowed high intake to be normalised and talk about no more than 2 glasses per day as though that is innocuous. Despite the many times we repeat the myth of beneficial aspects of alcohol, the safest intake level is zero standard drinks per week [54]. This major risk factor for dementia is also a risk factor for a large number of other physical and societal ills, being the 7th leading risk factor for deaths and loss of healthy years globally in 2016 [54]; it requires primordial prevention and a complete rethink around the availability and acceptability of alcohol at a national level as well as assistance with alcohol addiction and treatment of alcohol-related disorders [55].

Traumatic brain injury (TBI) makes a substantial contribution to the world's injury burden; it is caused primarily by falls and traffic injuries and is increasingly recognised as global health priority in view of its preventability and cost. In 2016, there were >27 million new cases of TBI globally, with an age-standardised incidence rate of 369 per 100,000 population and a prevalence of >55 million [56]. From 1990 to 2016, the age-standardised incidence and prevalence rates increased by 3·6% and 8·4% respectively [56]. In high-income countries (HICs), the number of elderly people with TBI is increasing, mainly due to falls; in low- and middle-income countries (LMICs), the increasing use of motor vehicles, motorcycles, and bicycles is associated with a higher incidence of traffic-crash injuries [57]. Thus, the burden of TBI is likely to continue to increase. Approaches to prevention are effective to varying degrees in HICs, particularly attention to traffic crashes and traffic-crash injury, via improved roads, improved vehicles, speed limits, driver training, reduction of driving while inebriated, seatbelts, helmets, etc [57]. There is increasing awareness of the preventability of falls among older people. Concussion/head-injury assessment and management by relevant staff on hand is being ramped up in contact sports [58]. However, this is all more poorly implemented in LMICs [57]. Furthermore and crucially, data on the impact of best management of the initial injury on subsequent risk of dementia are lacking and, as noted above, there are data to show that risk remains elevated even 30 years after the initial trauma [18].

The association with infection argues for careful attention to vaccine availability (against influenza, COVID-19, and whatever comes later) and uptake (particularly in LMICs), as well as greater emphasis on combatting misinformation regarding vaccines.

In summary, dementia is steadily increasing worldwide with major individual, family, societal, and economic consequences. Although treatment is currently largely ineffective and aspects of the underlying pathophysiology unclear, there is good evidence that much of it is preventable. That evidence should better inform policy.

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