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Viruses and pathological brain ageing: a challenge we must confront

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Abstract

The neuropathological mechanisms that lead to dementia start decades before the full expression of the disease, and even childhood brain and mental health play a role. It is therefore important to determine what are the risk factors for dementia across the life span. While a wide range of risk factors has been considered in clinical studies, the role of pathogenic viruses as unique or contributing risk factors has been relatively neglected. The COVID-19 pandemic has dramatically changed this situation. This article provides an introduction on how viruses may play a role in the aetiology of dementia highlighting the best researched example: Herpes Virus Simplex (HSV)-1. Next, relevant research in the HIV and COVID-19 epidemics is provided emphasising the complex interplay between acute, chronic, latent phases of the infection and the immune system in promoting pathological brain ageing. As both dementia and viral infections are global health issues, the compounding impact of socio-economic and health disparities in impacting the brain health of most vulnerable people is also stressed. Research on the impact of COVID-19 on brain health is nascent and should be informed by the existing knowledge of the brain health impact of other viral infections and post-viral syndromes, while taking advantage of the Australian leadership in infectious diseases research.

Introduction

Dementia is a global public health issue with impact increasing across the next decades because the global population is ageing (Dementia Forecasting Collaborators, 2022), but also because complex risk factors will come into play to potentially increase the global incidence of the condition further (Aung et al., 2019). This picture may be mitigated by early prevention and intervention (Barbera et al., 2023) as well as the availability of new treatments for Alzheimer's disease (AD) (Park et al., 2023). However, as for other global health issues, there are strong inequalities in access to dementia care (Kenning et al., 2017), intervention (Shaw et al., 2022) and dementia trials (Vyas et al., 2018). Only a small number of Low Middle-Income Countries (LMICs) have been the site for dementia trials (Salcher-Konrad et al., 2023).

It is estimated that the number of people with dementia will increase from 57.4 (95% uncertainty interval 50.4–65.1) million cases globally in 2019 to 152.8 (130.8–175.9) million cases in 2050 (Dementia Forecasting Collaborators, 2022). Besides non-modifiable risk factors (i.e., genetic risk, age), the 12 modifiable risk factors which were considered in this study to estimate projections of the global dementia prevalence in 2050 were: low education; hypertension; hearing impairment; smoking; midlife obesity; depression; physical inactivity; diabetes; social isolation; excessive alcohol con-

sumption; head injury; and air pollution. Critically, these predictions do not consider the impact of pathogenic viruses.

Amongst the very large number of viruses (~10^{31}) (Mushegian, 2020), some pathogenic viruses' role in causing severe acute neurological disorders is well described (Swanson and McGavern, 2015; Wouk et al., 2021). Typically, such viruses have high *neuroinvasiveness*, are *neuronotropic* or/and *neurotropic and highly neurovirulent* (e.g., human enteroviruses, alphaviruses, some flaviviruses such as Japanese encephalitis virus, West Nile virus) (Johnson, 1999; Swanson and McGavern, 2015). *Neuroinvasiveness* refers to a virus that can enter the central nervous system (CNS) or peripheral nervous system (PNS). A *neuronotropic* virus is a virus that can specifically infect neurons. A *neurotropic* virus is a virus can infect various brain cells. *Neurovirulence* refers to a virus that can cause a neurological disorder (Johnson, 1999).

Neurovirological symptomatology is highly varied (Swanson and McGavern, 2015; Wouk et al., 2021). It depends on the types of viruses (how it interacts with the host), the life cycle of the virus during acute, chronic, and latent phases of the infection and in the virus capacity to enter the CNS and/or PNS (i.e., neuroinvasiveness) as well as the route of neuroinvasiveness (e.g., blood stream, peripheral nerves, nasal mucosa and anterograde trafficking to the olfactory bulb, direct or "Trojan horse" entry through the blood brain barrier). Next the damage that a virus can cause is related to the specificities of its neurotropism and neurovirulence. Viruses that directly infect neurons and are typically highly neurovirulent and have the worst prognosis, especially in children (Swanson and McGavern, 2015). By contrast, viruses that have low tropism for neurons can lead to early onset dementia by infecting other cells in the brain, such as HIV which infects mainly microglia (Killingsworth and Spudich, 2022), the resident immune cells of the brain. A critical aspect that distinguishes acute and chronic neurological impact of viruses is also how the immune system within the brain and in the rest of the body responds to the presence of a virus (Swanson and McGavern, 2015). While an initial immune response can abrogate any health complications (e.g., most people with COVID-19 infection), an exaggerated immune response may lead to severe acute meningitis and encephalitis with long-term complications (e.g., stroke), as has also been described for SARS CoV-2 (Ellul et al., 2020). The acute immune response may also provoke a chronic immune dysregulation, where the long-term interactions of the virus with the immune system promote neuroinflammation (Wouk et al., 2021) — the latter being a major driver of neurodegeneration (Zhang et al., 2023). Some viruses establish long-term viral reservoirs (e.g., HIV, HSV-1, Epstein-Barr virus, cytomegalovirus) in various parts of the body. Under various circumstances, the latent virus can be reactivated, leading to a potential role in the development of chronic immune activation, inflammation and neuroinflammation (Wouk et al., 2021).

The impact of some pathogenic viruses on brain health is also contingent of their endemic, epidemic or pandemic status as well as the capacity to treat them with antivirals or prevent with vaccines. In any case, many viruses have large societal impact with greater health impact on the ageing population and other vulnerable people as seen during the COVID-19 pandemic, including in Australia (Australian Bureau of Statis-

tics, 2022). Even when antiviral treatment is available, as in the case of HIV infection, societal impacts continue as treatment access inequalities are not easily resolved (Ferguson et al., 2022). These considerations are important because dementia prevalence has regional variations (Dementia Forecasting Collaborators, 2022). The smallest percentage changes in the number of projected dementia cases between 2019 and 2050 are in high-income Asia Pacific (53% [41–67]) and western Europe (74% [58–90]), and the largest are in north Africa and the Middle East (367% [329–403]) as well as eastern sub-Saharan Africa (357% [323–395]). Relevant to the prevalence of viral conditions globally, these projected regional dramatic increases overlap with regions of the world where the HIV epidemic is the most prevalent and where other viruses are endemic (e.g., dengue and chikungunya). These regional variations are also important because of the way viruses interact with the immune system. In LMICs there is a higher rate of baseline immune compromise (Petoumenos et al., 2017), and higher background level of immune activation linked in part to a higher exposure to common viruses (Yap et al., 2017). As mentioned, viruses can directly injure the CNS, but viruses also perturb the CNS due to the immune response in the brain and other parts of the body. The consequence of this cascade of events is only partly understood, especially in relation to brain ageing, and the processes of brain injury that are known to cause dementia (i.e., vascular brain injury (Cysique and Brew, 2019)). Finally, with global climate change, more regions of the world will be impacted by endemic viruses (and other pathogens), and more frequently (Boguslavsky et al., 2022), further highlighting the importance of considering viruses as risk factor for dementia and brain health in general.

Globally prevalent pathogenic viruses and their role in the aetiology of dementia, Herpes Simplex Virus-1 (HSV-1) as a proof of concept

The hypothesis that viruses (and other pathogens such as parasites, bacteria, and fungi) play a role in the pathogenesis of dementia and AD is not novel. It dates to the early 1900 as proposed by Alois Alzheimer and Oskar Fischer (Vojtechova et al., 2022). In this regard, among the human herpesviruses, the best studied is HSV-1. HSV-1 is a neurotropic virus. Primary infection usually occurs during childhood and 60–70% of individuals under 50 years of age are infected with HSV-1 worldwide (Marcocci et al., 2020). After primary infection of epithelial cells, the virus becomes latent in neurons of the PNS and can be periodically reactivated. It then traffics to the CNS resulting in recurrent clinical or subclinical episodes throughout life. Repeated HSV-1 brain reactivation may result in neuronal damage that resembles the neurodegenerative mechanisms of AD, suggesting a unique and direct neuropathological role of the virus within the brain (Marcocci et al., 2020). HSV-1 reactivation triggers an inflammatory process, causing damage to the cells, along with formation of amyloid plaques and neurofibrillary tangles. Supporting a role of HSV-1 in the aetiology of AD are retrospective longitudinal studies, some with case-control designs (Marcocci et al., 2020) which show that anti-HSV antibodies in the plasma are associated with an increased risk of AD more than 6.6 years before diagnosis. Furthermore, clinical research shows that the historical

viral burden can impact current cognition, and that reactivation of HSV-1 due to age-related immune compromise is a dementia risk factor (Wouk et al., 2021). However, the significance of this research is hampered by retrospective analyses from cohort studies which were not initially designed to assess the question of virus-related brain injury, so that the strength of such results remains debated (Piotrowski et al., 2023). More interesting are findings which show that amyloid beta (the neurotoxic protein which accumulates to promote AD pathology, "the amyloid hypothesis" (Chen et al., 2017), is an antimicrobial peptide, protecting the brain against pathogens (Vojtechova et al., 2022). Recent *in vitro* and *in vivo* studies show that microbial infection can increase amyloid beta production and aggregation (Piotrowski et al., 2023). As such, in case of a prolonged or chronic immune activation, and especially in the context of an ageing immune system, amyloid beta accumulation and aggregation may promote (Vojtechova et al., 2022) or compound (Aung et al., 2019) neuroinflammation and eventually neurodegeneration.

Globally prevalent pathogenic viruses and their involvement in the aetiology of dementia — the case of HIV

Human immunodeficiency virus type 1 (HIV) is a lentivirus which primarily infects immune cells ($CD4^+$ memory T cells) leading to acquired immune deficiency syndrome (AIDS) if untreated. Without treatment neurological disorders are common as the disease progresses to AIDS (up to 50% including HIV-associated dementia, HIV-associated neuropathy, aseptic meningitis, seizures, vacuolar myelopathy, headache, and different movement disorders as well as opportunistic infections affecting the CNS) (Mohammadzadeh et al., 2023). With early treatment, severe neurological manifestations are rare. However, the prevalence of mild forms of neurocognitive deficits (called HIV-associated neurocognitive disorder: HAND) persists and is more frequent in people living with long-term infection and ageing, those with historical AIDS, and those with age-related comorbidities as well as those with greater mental health burden (Saloner and Cysique, 2017). Importantly, the greater frequency of age-related comorbidities is in part related to the chronic presence of HIV in the body, which is thought to be associated with chronic immune activation (Falutz et al., 2021). Other factors for greater frequency of age-related comorbidities in the HIV population include lifestyle (smoking, alcohol and substance use — higher than in the general population, the effect of widely used antiretrovirals which are toxic for cardiac and renal functions), and the effect of health disparities globally. HIV is treated with a lifelong combination of antiretrovirals suppressing the viral replication at several stages of the replication cycle. HIV is a retrovirus, meaning that it integrates into the host DNA. If the antiviral treatment is ceased or interrupted, replication of the virus rebounds within two weeks, demonstrating that the virus is only controlled by the treatment but not eradicated. Rebound is thought to originate from specific anatomical and cellular viral reservoirs in which viral DNA persists integrated into the host genome. There is a debate as to what extent the brain represents a competent and partly separate viral reservoir, although there is increasing evidence that the CNS harbours competent proviruses — that is, HIV DNA

capable of starting to replicate if treatment is interrupted (Mohammadzadeh et al., 2023).

HIV enters the CNS soon after infecting the rest of the body directly or via a Trojan horse mechanism carried by infected T cells through the blood brain barrier. Without treatment, the activated resident immune cells, microglia, lead to severe brain inflammation and eventually neuronal death. Moreover, monocytes and macrophages continue to transport HIV into the CNS during chronic infection (Gelman, 2015). With treatment and viral suppression, T-cell infiltration of the CNS may include resting memory T-cells and represent another CNS cellular reservoir for HIV. Recent research also shows that a small proportion of astrocytes may also be cellular reservoirs for HIV (Mohammadzadeh et al., 2023). Very recent research from an Australian group (Angelovich et al., 2023) shows intact proviruses are primarily found in the brain frontal white matter but also detected in other brain regions, demonstrating that the brain is a major reservoir of intact and potentially replication-competent HIV DNA that persists despite antiretroviral therapy. Nevertheless, replication of this research is needed. The persistence of HIV in the CNS can lead to neuroinflammation, and there is also evidence that it is associated with increases vascular brain injury. In fact, evidence for increased risk of AD is low in people with suppressed HIV infection, however evidence for increased cardiovascular and cerebrovascular diseases is high, and thus represents a much more likely neuropathological mechanism of brain ageing than AD-like neurodegeneration (Cysique and Brew, 2019). However, this research only includes individuals aged their mid-fifties; therefore, a note of caution is warranted, as studies in people with HIV infection in their seventies do not yet exist, and it is well recognised that vascular brain injury at that age is a major risk factor for dementia in the general population (Chowdhary et al., 2021). Systemic (impacting the brain-blood-barrier function (Galea, 2021)) and brain-based chronic immune activation is well described in people living with HIV, despite successful antiretroviral treatment (Ulfhammer et al., 2018). This process is now considered lifelong, as the first generation of people living with HIV now reaching old age has been infected for 40 years. Within the brain, there is evidence that residual HIV replication is possible, because the brain is "separated" from the rest of the body by the blood brain barrier and because antiretrovirals do not all penetrate the CNS in sufficient concentrations (Dahl et al., 2014). Although this is less likely with the most modern treatment (Mohammadzadeh et al., 2023), this is not available to most people living with HIV across the world who commonly still receive less CNS effective therapies, but also more toxic therapies for longer (Vos and Venter, 2021).

In this context, my research group and others are assessing whether HIV infection may be a potential model of premature, accentuated, and accelerated chronological and biological ageing — *ageing being the number one risk factor for dementia* (Aung et al., 2019). Premature cognitive ageing is younger-onset cognitive impairment as compared to same-age controls, while accentuated cognitive ageing refers to greater severity of cognitive impairment compared to same-age control (Aung, Aghvinian, et al., 2021). The strongest evidence for premature and accentuated ageing of

brain function in people living with HIV comes from neuroimaging research which cumulatively shows that the brain structural health (i.e., lower and less complex structural volumes), the brain bioenergetics, neuroaxonal health and vascular health are not only more impacted on as a function of age and HIV status, but are also more likely to present clinically significant deterioration than age-matched controls (Boerwinkle et al., 2021; Pfefferbaum et al., 2018; Samboju et al., 2021). When considering truly accelerated brain ageing, representing a synergism (i.e., cognitive ageing is worsening over time in people living with HIV more so than in age-matched controls (Aung, Aghvinian, et al., 2021)), there are results showing no acceleration of brain ageing (Cole et al., 2018) in cohorts aged in their mid-50s, but concerningly more recent data in people living with HIV aged 60+ show accelerated brain ageing (Pfefferbaum et al., 2018). Overall, in terms of cognitive ageing, while the literature was initially more mixed (Aung, Aghvinian, et al., 2021), there is now increasing evidence for a premature ageing effect (Aung, Bloch, et al., 2021; Aung et al., 2022). More evidence for accelerating cognitive ageing will require large samples and long-term follow-up in people reaching the exponential age of dementia increased (i.e., 65+) (Aung, Aghvinian, et al., 2021). Furthermore, in the context of highly morbid cohorts (poverty, multiple health disparities, chronic trauma, high level of psychiatric and substance use in addition to age-related multimorbidity and co-infection mainly to Hepatitis C virus), detecting premature, accentuated, or accelerating ageing is challenging (Heaton et al., 2022) and has led some to state that comorbidities explain all issues of brain ageing in people with HIV, but not HIV itself when it is treated (Nightingale et al., 2014). However, in such instances, the effects of age-related and other comorbidities likely mask any HIV-related chronological age effect, as these comorbidities are linked to biological ageing (Mehta et al., 2021).

The role of the viral reservoirs in the promotion of abnormal cognitive ageing in people with HIV remains to be specifically studied, but there is evidence that ongoing viral activity in the cerebrospinal fluid is associated with brain injury (Suzuki et al., 2022). As a model of abnormal ageing, chronic and persistent HIV infection can be conceived as a "multi-hits" model, and can inform understanding of other types of viral infection in how they may lead to, or promote, dementia (Al-Harthi et al., 2020). In such models (Aung et al., 2019), the life cycle of the virus (acute, chronic, latent, reactivation, reactivation of other viruses, co-infections) and the timing of treatment (early/late) across the life span (senescent immune system, rise of dementia in the general population) is hypothesised to contribute to both non-modifiable (mainly age, background neuro/inflammation, interaction with genetic factors) and modifiable factors relevant to the HIV population globally (education, cardiovascular and other age-related systemic diseases, life style such as smoking, alcohol and substance use, mid-life metabolic changes partially linked to the duration of toxic antiretroviral use, high mental health burden, social isolation and stigma worsened by ageing, and health disparities). It is critical that this research receives continued support as 37 million people are living with HIV worldwide, most of them in LMICs. Lastly, research in people entering their 70s will be needed as these ages are associated with exponential

prevalence of dementia in the general population. Members of the HIV community and some researchers are worried about the added stigma of dementia risk in people living with HIV (Nightingale et al., 2023), but my research group (Aung et al., 2023) and others internationally believe that early detection and prevention as for the general population represents the best strategy to minimise a potential major public-health issue and added suffering for ageing people living with HIV. In this context, a larger part of the HIV community has called for urgent support and funding of aged care services in people who are ageing with HIV (International Coalition of Older People with HIV (iCOPe HIV), 2022).

Globally prevalent pathogenic viruses and their involvement in the aetiology of dementia — the case of SARS CoV-2

Early in the pandemic, neurologists and neuropsychologists with expertise in infectious diseases recognised that SARS CoV-2 had more than respiratory consequences (Cysique et al., 2021; Ellul et al., 2020). COVID-19-related encephalopathies and cerebrovascular disorders are one of the most significant acute neurological complications of SARS CoV-2 (Singh et al., 2022). Such acute viral conditions have a long-term impact on the overall and brain health of patients, while a history of strokes is a known dementia risk factor (Kuzma et al., 2018). As such, it is not surprising that SARS CoV-2 infection has been associated with rapid progression of dementia in individuals with pre-existing cognitive impairment (Dubey et al., 2023). This is to be understood in the context where people with dementia are more likely to contract COVID-19 due to difficulties in understanding and maintaining safe COVID-19 practices, being in nursing homes, and social isolation (Quan et al., 2023). Besides having a history of COVID-19 infection, factors linked to the COVID-19 pandemic — reduced exercise, increased alcohol use, social isolation, depressive symptoms, mild cognitive impairment — have been associated with cognitive decline in older adults (Corbett et al., 2023).

A systematic review and meta-analysis on added dementia risk in people who had COVID-19 shows that SARS-CoV-2 infection may be associated with a higher risk of AD, dementia, and Parkinson disease in post-COVID-19 survivors, compared with contemporary controls and other respiratory tract infections (i.e., influenza) (Rahmati et al., 2023). SARS-CoV-2 infection may also be associated with a higher risk for new-onset neurodegenerative diseases in recovered COVID-19 patients. Moreover, this review shows that individuals aged ≥65 years and infected with SARS-CoV-2 have a larger risk difference than those aged <65 years for developing dementia, corroborating the interaction between chronological age, viral infection, and dementia risk. Interestingly, the review did not find that being hospitalised or admitted to ICU represented a risk factor for dementia, but caution should be used in interpreting these results, as they are likely affected by survivor bias. In addition, most of the reviewed studies included patients from the early wave of the pandemic (Alpha, Delta). Most studies had also a short follow-up period (i.e., 3 months–2 years) — much shorter than what is needed to study dementia conversion, especially in consideration of the heterogeneity of patients involved and varied methodological assessments. In fact, the new-onset risk

was only derived from four original studies. Altogether, more research is needed to determine whether SARS CoV-2 uniquely contributes to new-onset neurodegenerative diseases (Charnley et al., 2022).

Viruses of the Coronaviridae family such as SARS-CoV-2 are single-stranded RNA viruses for which RNA can persist long-term (weeks–months) in a small minority of individuals, although intact virions and hence replicating virus is not found (Chen et al., 2023). Amongst the coronaviruses, SARS CoV-2 is one the most neuropathogenic because SARS-CoV-2 enters recipient cells by the binding of its spike protein to the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed by many cell types across the body and the brain (Granholm, 2023).

At least 90% of individuals who contract SARS CoV-2 are asymptomatic or develop a mild to moderate flue-like illness with primarily respiratory symptoms with recovery within 12–14 days. Risk of hospitalisation is lower with Omicron than earlier variants (0.55 (95% 0.23–1.30)) (Relan et al., 2023), which may be in part explained by raised immunity due to vaccinations and previous infections. Some studies have found that up to 20% of symptomatic, infected, unvaccinated adults need hospitalisation. Vaccinated individuals are 10 times less likely of developing a severe acute COVID-19 illness. The prevalence of severe COVID-19 illness requiring hospitalisation varies by countries, regions, age of the population and other health factors including vaccination uptake (Guzman-Esquivel et al., 2023).

Non-severe acute illness is characterised by a healthy innate immune response that aims at killing the virus, restricts its spread across the body, and induces an optimal adaptive immune response (i.e., production of antibodies capable of neutralising the virus). In individuals who develop a severe response, the innate immune response is excessive (i.e., cytokine storm) and can lead to multi-organ damage through acute respiratory distress syndrome (ARDS) and systemic hyperinflammation (Harne et al., 2023). Severe neurological consequences affect one-third in hospitalised individuals, and are characterised by severe brain inflammation (i.e., encephalopathy) and cerebrovascular diseases (e.g., ischemic stroke) (Singh et al., 2022). While there is evidence that SARS CoV-2 enters the brain, it is in relatively low quantities, meaning that it is not a highly neuroinvasive virus; however, it can infect many brain cell types, as the ACE2 receptor is ubiquitous. Severe acute neurological illness has been associated with the degree of brain infection (Granholm, 2023). Therefore, in most infected people who develop a mild to moderate acute illness, SARS CoV-2 association with brain changes is considered most likely to be mediated indirectly through the engagement of the immune system. As such, it is thought that peripheral immune activation can lead to neuroinflammation via disruption of the blood brain barrier function (Galea, 2021).

In most people, SARS CoV-2 infection resolves after about two weeks, and many are asymptomatic. By contrast, about 10–20% have persistent symptoms consistent with a post-viral syndrome that lasts from 3 months to several years. Post-viral syndromes before the advent of the COVID-19 pandemic have been well described (Sandler et al., 2021), so that this knowledge and related expertise can fast-forward research into Long COVID. The World Health Organisation

(WHO) defined Long COVID for clinical purposes as: continuing or new symptoms at least 3 months from the onset of COVID-19 infection that last at least 2 months and cannot be explained by an alternative diagnosis (World Health Organization, 2021). The most common symptoms include: fatigue with a post-exertional exacerbation (post-exertional malaise); "brain fog" including memory and attention deficits; sleep disturbance; breathlessness and other respiratory symptoms; abdominal pain; and other gastric symptoms. Risk factors for Long COVID include: female gender; being aged 20–50 years; having more severe initial disease or other medical comorbidities; and being from a vulnerable population (Chilunga et al., 2023).

Most recent studies estimating the prevalence of Long COVID in Australia state that they have used the WHO definition, but they have done so using different tools, producing various rates depending on the sample and ascertainment methods. Furthermore, the WHO definition is a clinical definition which aims at managing Long COVID and related symptoms independently of the specific aetiology, which means that this definition cannot strictly exclude non-COVID causes of Long COVID. A more robust research definition is needed as advocated by the Australian Partnership for Preparedness Research on Infectious Disease Emergencies (APPRISE Long COVID Initiative, 2023) and grounded into the post-infective/post-viral syndrome framework which has validated assessment tools and methods to classify post-viral syndrome such as Long COVID including into specific symptomatic clusters (Sandler et al., 2021). One Western Australian study yet to be peer-reviewed shows an 18% prevalence in a vaccinated post-Omicron infection cohort (Mulu et al., 2023). A study from Queensland found that 21.4% of post-COVID individuals had ongoing symptoms and that this was not different from those with influenza (23.4%). International data show that persistent symptoms after COVID-19 are higher in COVID than influenza cases, but this is in hospitalised patients (Xie et al., 2024). Another study of patients accessing a national digital mental health service found a Long COVID prevalence of 10% (Staples et al., 2023). The frequency of ongoing symptoms appears lower in children and adolescents (8% in Say et al., 2021). Furthermore, vaccinations, infection-associated immunity, and the availability of antiviral treatments are contributing to less severe acute COVID and less frequent Long COVID (Howe et al., 2023). However, international data also shows that the risk of Long COVID remains and may be increased with repeat infections (Bowe et al., 2023). Again, more definitive research is needed and coordinated at the national level to optimally estimate this new health condition (APPRISE Long COVID Initiative, 2023) using robust research methods to carefully exclude non-COVID-related symptoms, which are otherwise common in the general community (van der Maaden et al., 2023). Internationally, researchers are also working to develop a robust research case definition of Long COVID with the hope of developing targeted treatment (Thaweethai et al., 2023).

Most people with Long COVID are individuals of working age, hence the socio-economic impact is substantial. In the absence of Australian health economic data, it is noteworthy that the total economic cost of Long COVID in the US was

estimated at US$3.7 trillion (Cutler, 2022). The condition is associated with substantial disability, with an Australian Omicron-era study estimating 5200 years lived with disability (YLDs) attributable to Long COVID, greatly outweighing the 1800 years attributable to acute COVID (Howe et al., 2023). Further, qualitative research in the UK has revealed that individuals with Long COVID are severely impacted by their symptoms, heavily constrained in participating in their daily activities, and experience reduced quality of life, including negative impacts on mental health (Owen et al., 2023).

Mild cognitive difficulties (brain fog, memory, and attention deficits) are a major component of Long COVID and need to be differentiated from the acute neurological impact of COVID-19 infection which represents a severe COVID-19 complication. The mild cognitive difficulties of Long COVID do not represent a severe neurological complication, and new evidence suggests that it is another type of post-viral syndrome (Verveen et al., 2022). Long COVID-associated mild cognitive difficulties may nevertheless have a significant functional impact, as most people with the condition are of working age. Evidence for Long COVID cognitive difficulties being associated specifically with adverse impact on functional outcomes arises from our research (Cysique et al., 2023), where at four months post-infection, 22% of those with Long COVID and mild cognitive difficulties had not returned to their pre-COVID work or normal activities of daily living.

As for other infectious diseases with brain impact, in which my research team and collaborators have vast experience (Cysique and Brew, 2019; Smail and Brew, 2018), the pathogenesis of Long COVID cognitive difficulties is likely multifaceted (Wesselingh, 2023), primarily including immune dysregulation, autoimmunity, microthrombi, and some level of blood-brain barrier impairment. This pattern of chronic immune dysregulation and subtle vascular injury is reminiscent of chronic HIV-related brain injury, which is associated with low-grade neuroinflammation. Our research (Cysique et al., 2023) and that of others (Kavanagh, 2022) support a neuroinflammatory axis to the condition. Our results pinpoint the kynurenine pathway (KP) as a likely mediator of SARS CoV-2-related mild cognitive impairment. The KP is an interferon-stimulated tryptophan degradation pathway, important in immune tolerance, neurotoxicity, and vascular injury (Jones et al., 2015; Lovelace et al., 2017). The KP — including quinolinic acid, 3 hydroxy-anthranilic acid, kynurenine, and tryptophan (and ratio) — showed a *prolonged* (2 to 8 months) activation. The pattern of activation of the KP was associated with poorer cognition and greater likelihood of mild cognitive impairment over time. Importantly, no other blood biomarkers, sex, or clinical factors (pre-existing mental health or mental health during the study period, olfaction, medical comorbidities, disease severity or respiratory function) were associated with cognition. Furthermore, the biological plausibility for a role of the KP in the pathogenesis of Long COVID and associated cognitive difficulties is supported by recent findings across both basic (Wong et al., 2023) and clinical research (Collier et al., 2021; Holmes et al., 2021), including with prolonged activation which may make it more specific to Long COVID than acute COVID (Guo et al., 2023). Lastly, SARS-CoV-2 can efficiently

infect macrophages but leads to an abortive infection, and macrophages are a prominent feature of the neuropathology of COVID-19 (Balcom et al., 2021).

Conclusion

It took ten years between the discovery of HIV and the development of an internationally accepted definition of AIDS by the USA CDC in 1993. The situation with Long COVID has some similarities, although SARS CoV-2 and HIV have different neuro/pathogenesis. Such efforts require both national and international coordination as preconised by WHO (World Health Organisation (WHO), 2023). A large, nationally coordinated Long COVID study is needed in Australia, as determined by the Parliamentary enquiry into Long COVID (Parliament of Australia, 2023), like those that exist in the US, Canada, or the UK. In Australia, this is represented by the APPRISE and its OUTPOST prospective cohort "OUTcomes POST COVID", which will be recruited through existing primary care networks from June 2024 (APPRISE Long COVID Initiative, 2023). This research will be critical in determining whether Long COVID may be associated with pathological brain ageing in Australians. With the rationale of HSV-1 and HIV in promoting pathological ageing, there is a strong argument that dedicated research funding is needed for this endeavour beyond that of the Long COVID questions. Australia has in fact been a leader in infectious diseases research, with a major role to be supported across the Asia-Pacific region. The COVID-19 pandemic shows that viruses' impact on brain health with critical consideration for dementia risk research are challenges we must confront.

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