Subject heading: Dementia

Are severe infections a gateway to dementia?

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Abstract

A new study in *Nature Aging* on electronic health records from 1.7 million New Zealanders reveals that most patients with dementia have a history of hospital-treated infection. In a dementia-free population, individuals with a severe infection were at threefold higher risk of dementia even 25 years later.

Main

While individuals with severe infections experience a higher likelihood of developing dementia later in life, the underlying reasons for this association remain a subject of debate. An early hypothesis suggested that dementia may be an infectious disease caused by a pathogen. This 'germ' hypothesis was supported by observations that Alzheimer's disease is more common in groups of individuals who are in contact with dementia patients, such as spouses and neurosurgeons.[1] More recently, researchers have proposed that infections may represent a risk factor for dementia (the 'infectious hypothesis') or that infections accelerate the progression of dementia pathology already underway (the 'infectious-accelerant theory').[2]

However, there are also more skeptical views. According to them, the association may be an artefact arising from reverse causation where increased vulnerability to severe infections is the consequence of preclinical dementia rather than a cause. A further possibility is that the link is driven by a third factor, such as shared genetics between susceptibility to infections and dementia, accelerated biological ageing contributing to both age-related immune-senescence and neurodegeneration, or an underlying condition both compromises immune function and increases dementia risk (e.g. diabetes, cardiovascular disease or depression). If these scenarios were true and accounted for the entirety of the observed infection-dementia relationship, the link between infections and dementia would be spurious.

In this issue of *Nature Aging*, Richmond-Rakerd *et al.* investigate associations of hospital-treated infections with subsequent dementia in a nationwide study from New Zeeland.[3] Using electronic

records from national health registries, the authors identified individuals born between 1929 and 1968 and followed them from 1989 to 2019. The study population included a total of 1.7 million participants aged 21 to 60 years at baseline. Dates and diagnoses of infections were obtained from hospital admission records. For dementia ascertainment, data from mortality and pharmaceutical registries, in addition to hospitalisations, were used. In this extensive study with a 30-year follow-up, more than 465,000 individuals experienced infections and 37,000 developed dementia. The median age at the first infection diagnosis was 9.3 years before the median age of dementia diagnosis. The authors found that among individuals diagnosed with dementia, 66% had a history of infections, compared to 26% in individuals without dementia. Furthermore, those with an infection diagnosis had a 2.9-fold higher risk of subsequent dementia (95% CI 2.7–3.2) compared to those without an infection diagnosis. These findings are consistent with those reported from other large-scale cohort studies from Europe and the US.[4]

Furthermore, Richmond-Rakerd et al. conducted a series of supplementary analyses, providing valuable insights that should be interpreted in light of existing evidence.[3] Firstly, Alzheimer's disease pathology typically manifests 1 to 2 decades before clinical symptom onset, posing challenges in determining whether increased susceptibility to infections contributes to or reflects dementia pathogenesis. Previous analyses from a multicohort study involving 200,000 participants have shown that the association between hospital-treated infections and dementia persists even when restricted to cases where dementia develops more than 10 years after the infection. [5] However, this does not entirely rule out the possibility of reverse causation. In their study, Richmond-Rakerd and colleagues addressed this limitation by stratifying the 30-year follow-up period into 5-year intervals.[3] Their findings indicate that the heightened risk remains consistent across all follow-up intervals, ranging from 1-5 years (hazard ratio 2.5, 95% CI 2.3–2.6) to 25-30 years (hazard ratio 3.6, 95% CI 3.1–4.2). This suggests that reverse causation is an unlikely explanation for the observed link.

Secondly, Richmond-Rakerd et al. conducted several analyses to mitigate the influence of third factors.[3] These included adjusting for pre-existing physical diseases and mental disorders through multivariable models, such as diabetes, stroke, coronary heart disease, gout, COPD, cancer, traumatic brain injury, mood and neurotic disorders, substance use disorders, and psychotic disorders. Additionally, the authors stratified the analyses by birth year to assess whether the observed link persists at younger ages, where age-related changes in the immune system, such as up-regulation of pro-inflammatory signalling and reductions in naïve lymphocytes, antibody effectiveness, and phagocytic capacity, are not yet prevalent, and chronic conditions compromising the immune system are rare. The main finding remained consistent across all these analyses. Although each of these analyses provided additional support for infection's role as a dementia risk factor, the potential explanatory effect of genetic variants jointly associated infection vulnerability and dementia risk, as well as other factors, such as advanced immune age, could not be ruled out.

Thirdly, much research has centred on specific infections or sets of pathogens, with a particular emphasis on viruses known to cross the blood-brain barrier—a critical structure shielding the brain from harmful substances in the bloodstream. These neurotrophic pathogens include, for instance, herpes simplex and human immunodeficiency viruses, both implicated in increased dementia risk.[2] However, recent epidemiological studies covering a wide range of infections have revealed that hospitalisation for nearly any infection is associated with heightened dementia risk, showing little specificity for the type of infection and including both central nervous system (CNS) and extra-CNS

infections.[5-8] This observation was corroborated by Richmond-Rakerd et al. They found no significant differences in effect estimates between viral, bacterial, parasitic, or other infections.[3] Taken together, these findings indicate that not only brain infections, but also infections that occur outside the CNS, are linked to an elevated risk of dementia. Therefore, rather than pursuing a specific major dementia-causing pathogen, research should prioritize understanding the mechanisms shared by severe infections that may increase dementia risk. It is worth noting that mild infections are not consistently associated with dementia risk.[6]

How do infections increase the risk of dementia? One hypothesis suggests that the underlying mechanisms involve the brain's response to neurotrophic pathogens. In this scenario, infectious agents penetrate the CNS, activate the brain's immune response in a manner which promotes sustained neuroinflammation, resulting in downstream neurodegenerative damage (e.g., excessive synaptic pruning, neuronal apoptosis; *Figure 1*).[4,9] However, the findings presented by Richmond-Rakerd et al. and the findings from a long list of previous studies suggest that pathogens need not enter the CNS to have deleterious effect on brain function. Acute infections that occur outside the CNS typically trigger an innate immune response characterized by the expression of immune signalling molecules, such as cytokines and chemokines, at or near the site of infection. Although cytokines and chemokines are produced outside the CNS in this context, these molecules can exert an effect within the CNS though a number of conduits, including via the blood-brain barrier (which becomes more permeability during acute infections), through the meningeal lymphatic system, via the choroid plexus, and as an indirect consequence of brain endothelial cell activation. Through each of these components of the neuro-immune axis (*Figure* 1), severe peripheral infections may cause an influx of inflammatory mediators and immune cells into the brain parenchyma, contributing to neuroinflammation. A third pathway could involve mechanisms where peripheral immune challenge leads to the suppression of perivascular flow of cerebrospinal fluid (i.e., glymphatic drainage), impairing the clearance of potentially neurotoxic waste products from the CNS to the peripheral immune system. However, human evidence for this mechanism is limited. Additionally, epidemiological studies have suggested that vascular mechanisms may play a role, as the association of severe infections is stronger for vascular dementia than for Alzheimer's disease[5]—a finding also replicated in the study by Richmond-Rakerd *et al*.[3] Specific mechanistic explanations for the link between infection and vascular-mediated cognitive decline include endothelial dysfunction and thrombosis secondary to acute inflammation, infection-related platelet aggregation, and accelerated accumulation atherogenesis.[10]

Richmond-Rakerd *et al.* conclude their paper by suggesting that effective prevention of infections might reduce the burden of dementia.[3] Although there is no consistent evidence from larger randomized controlled trials to demonstrate that targeting infection and inflammation would be effective in reducing cognitive impairment or the risk and progression of dementia,[11] epidemiological studies suggest that vaccination against certain infections (e.g., varicella zoster virus) may reduce dementia risk.[12] Before specific prevention or treatment recommendations can be made, more work is needed to understand the unifying mechanisms that jointly link multiple infection types to enhanced dementia risk. Although systemic inflammation has been proposed as a potential unifying mechanism, anti-inflammatory trials on non-steroidal anti-inflammatory medications, such as naproxen and celecoxib,[13] as well as minocycline, a tetracycline antibiotic[14] have reported null findings. To the degree that systemic inflammation is a common risk factor for dementia onset among those with an infection history, more targeted approaches to immunomodulation of specific

implicated pathways (e.g. cGAS-STING) may prove more efficacious than broad immunosuppression. Big data in combination with modern genetic and causal inference methods have already shed some light on this issue. For example, recent Mendelian Randomization analyses suggest that specific immune cell types and proteins associated with autoimmunity might be a modifiable component in dementia-causing diseases.[15] Yet, to date, this hypothesis has not been tested in clinical trials.

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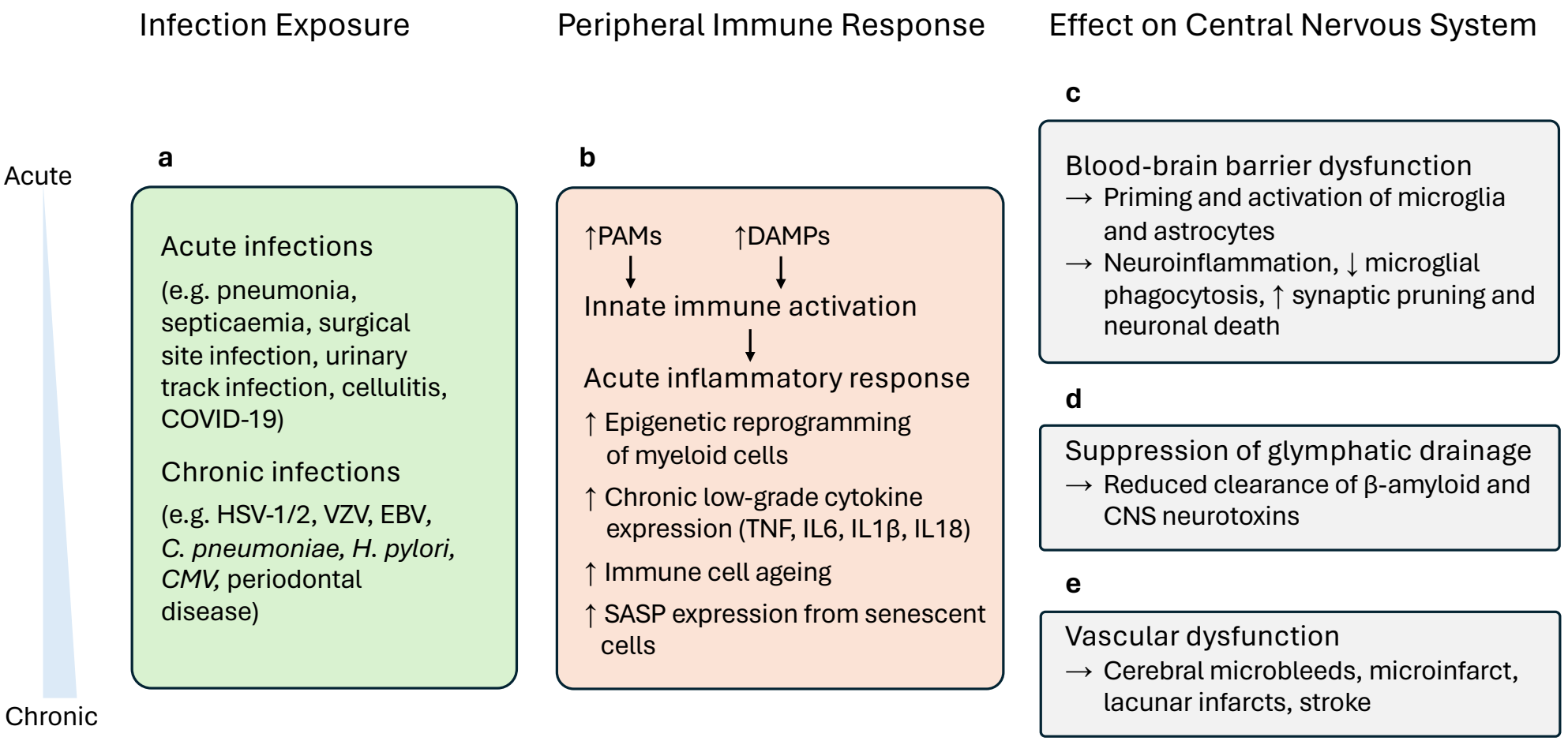
Competing interests

The author declares no competing interests.

Figure legend

Fig 1 | Mechanisms linking infections and increased risk of dementia
a,b, Richmond-Rakerd et al. observed that a broad spectrum of severe infections, including both CNS and extra-CNS infections, was linked to an increased risk of dementia. This confirms prior epidemiological findings that have shown limited specificity regarding the type of infections associated with dementia risk (**a**). Thus, it is plausible that peripheral immune responses which are common across various severe infections (**b**) may contribute to the heightened risk of dementia. **c,d,e,** Richmond-Rakerd et al. also found a link between infections and all the examined subtypes of dementia, with a stronger association observed for vascular dementia compared to Alzheimer's disease. This is consistent with general explanations for increased dementia risk in relation to infections, such as blood-brain barrier dysfunction (**c**) and suppression of glymphatic drainage (**d**), as well as evidence that emphasises vascular mechanisms (**e**). *Abbreviations*: C. pneumoniae, Chlamydia pneumoniae; CNS, central nervous system; CMV, cytomegalovirus; DAMPs, damage-associated molecular patterns; EBV, Epstein-Barr virus; H. pylori, Helicobacter pylori; HSV, herpes simplex virus; IL, interleukin; PAMPs, pathogen-associated molecular patterns; SASP, Senescence-Associated Secretory Phenotype; TNF, tumour necrosis factor; VZV, varicella zoster virus.


Infection Exposure
Peripheral Immune Response
Effect on Central Nervous System
Acute
Chronic
a
Acute infections
(e.g. pneumonia, septicaemia, surgical site infection, urinary track infection, cellulitis, COVID-19)
Chronic infections
(e.g. HSV-1/2, VZV, EBV, C. pneumoniae, H. pylori, CMV, periodontal disease)
b
↑PAMs
↑DAMPs
Innate immune activation
Acute inflammatory response
↑ Epigenetic reprogramming of myeloid cells
↑ Chronic low-grade cytokine expression (TNF, IL6, IL1β, IL18)
↑ Immune cell ageing
↑ SASP expression from senescent cells
c
Blood-brain barrier dysfunction
→ Priming and activation of microglia and astrocytes
→ Neuroinflammation, ↓ microglial phagocytosis, ↑ synaptic pruning and neuronal death
d
Suppression of glymphatic drainage
→ Reduced clearance of β-amyloid and CNS neurotoxins
e
Vascular dysfunction
→ Cerebral microbleeds, microinfarct, lacunar infarcts, stroke