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REVIEW ARTICLE

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Developmental priming of early cerebrovascular ageing: Implications across a lifetime

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Abstract

Introduction: Neurological conditions such as Alzheimer's disease and stroke represent a substantial health burden to the world's ageing population. Cerebrovascular dysfunction is a key contributor to these conditions, affecting an individual's risk profile, age of onset, and severity of neurological disease. Recent data shows that early-life events, such as maternal health during pregnancy, birth weight and exposure to environmental toxins can 'prime' the vascular system for later changes. With age, blood vessels can become less flexible and more prone to damage. This can lead to reduced blood flow to the brain, which is associated with cognitive decline and an increased risk of stroke and other cerebrovascular diseases. These in turn increase the risk of vascular dementia and Alzheimer's disease.

Objectives: We aim to explore how early life factors influence cerebrovascular health, ageing and disease.

Methods: We have reviewed recently published literature from epidemiological studies, clinical cases and basic research which explore mechanisms that contribute to cerebrovascular and blood-brain barrier dysfunction, with a particularly focus on those that assess contribution of early-life events or vascular priming to subsequent injury.

Results: Perinatal events have been linked to acute cerebrovascular dysfunction and long-term structural reorganisation. Systemic disease throughout the lifetime that produce inflammatory or oxidative stress may further sensitise the cerebrovasculature to disease and contribute to neurodegeneration.

Conclusions: By identifying these early-life determinants and understanding their mechanisms, scientists aim to develop strategies for preventing or mitigating cerebrovascular ageing-related issues.

KEYWORDS
ageing, blood-brain barrier, development, inflammation, sensitisation

Abbreviations: BBB, blood-brain barrier; CBF, cerebral blood flow; CVD, cerebrovascular disease; IQ, intelligence quotient; LPS, lipopolysaccharide; MRI, magnetic resonance imaging; MS, multiple sclerosis; SVD, small vessel disease.

Key points

- Early-life events, such as low birth weight or preterm birth, can increase an individuals' risk of cerebrovascular and neurodegenerative disease.
- Perinatal inflammation or oxidative stress can cause short-term changes in vascular tone and blood-brain barrier (BBB) function.
- Altered angiogenesis and cerebrovascular structure also occur and may sensitise the brain and cerebrovasculature to subsequent injury.
- More work is required to understand mechanisms of injuries and find biomarkers to predict risk or therapeutic potential.

1 | INTRODUCTION

Blood supply to the brain, providing essential nutrients and removing metabolic waste, is facilitated by the dynamic actions of the cerebrovasculature. As with other vessels in the body, endothelial cells form the lumen of the cerebral blood vessels, reacting to circulating mediators and physically and chemically interacting with surrounding contractile cells to allow local regulation of cerebrovascular function.[1] Distinct from other vascular beds, however, is the specialisation of the endothelial cells that create the blood-brain barrier (BBB); a physical barrier mediated by paracellular junctions in combination with an array of active influx and efflux transports and signalling mechanisms that is essential for maintaining brain homoeostasis.[1,2] For many years there was a belief that the brain was an immune-privileged site and that the BBB contributed to this status. However, it is now clear that neurological injury is associated with inflammatory processes and that there is signalling across the BBB that can both modulate neurological injury and allow systemic assessment of disease status.[3] Moreover, there is increasing evidence that disruption in cerebrovascular function, be that regulation of cerebral blood flow (CBF), BBB integrity or signalling across the endothelium, can exacerbate neurodegenerative disease[1,4] and may even be part of the disease aetiology in some conditions.[1,5] Here we explore the value in casting our scientific eye even early in the disease process, considering the potential contribution of systemic disease and early-life events to the functioning of the cerebrovasculature. By doing so, we hope to identify mechanisms of dysfunction that could be utilised as biomarkers or therapeutically targeted to prevent serious vascular disease and its neurological sequels.

1.1 | Associations between vascular function and neurodegenerative disease, and mid-life risk factors

Links between cerebrovascular function and neurological diseases such as stroke and vascular dementia are well established,[4,5] and have recently been broadened to other neurodegenerative disease with numerous studies showing BBB disruption in postmortem Alzheimer's disease brains,[6] and correlation between Alzheimer's disease and other measures of poor cardiovascular health.[5] Over the last 10 years, neuroimaging methods have detected a trajectory of BBB breakdown and cardiovascular disruption in ageing, and cases of cognitive impairment, well before the development of disabling clinical signs. For example, two small clinical studies using dynamic enhanced magnetic resonance imaging (MRI; movement of Gadolinium contrast agent adjusted for CBF) to measure BBB permeability in individuals with an early Alzheimer's diagnosis compared to age-matched controls, showed increased permeability in the patient group,[7,8] with measures of increased permeability correlating with cognitive decline.[7] Pericytes in the neurovascular unit are important for regulating local blood flow and supporting BBB properties of the cerebral endothelial cells. Reduced pericyte actions have been associated with altered vascular function in neurodegenerative disease. Postmortem studies using intracerebral fibrinogen as a marker of BBB breakdown, have shown a significant decrease in the pericyte marker PDGFRβ correlated with an increased fibrinogen level that also correlated with amyloid-β plaque load in brains from Alzheimer's disease patients,[9] and decreased pericyte coverage of white matter vessels in post-stroke dementia, vascular dementia and brains for Alzheimer's disease patients.[10] Separately, in a larger imaging study, Freeze, et al.[11] correlated BBB transit, measured with MRI, with MRI features of small vessel disease (SVD, e.g. white matter hyperintensities, lacunas, microbleeds and increased perivascular space) and cognitive capacity in normally ageing individuals, as well as those with mild cognitive impairment and Alzheimer's disease. SVD has been strongly associated with cognitive decline[12] in its own right, with the hypothesised mechanism being that reduced CBF and endothelial dysfunction contribute to the MRI-detectable pathologies and that the cognitive impairment related to these is at least partly due to disruption of white matter tracts that are critical for integrated and timely cognitive function.[12] SVD may, therefore, exacerbate early Alzheimer's disease pathology via these aligned mechanisms. Collectively these studies suggest that loss of pericytes, altered regulation of blood flow and increased BBB permeability occur naturally in ageing and may be exacerbated in the early stages of cognitive impairment, when they directly contribute to reduced processing capacity.

The 2023 update on heart-disease and stroke by the American Heart Association,[13] found that individuals with chronic high blood pressure (hypertension), heart disease, stroke and diabetes were at a greater risk of an early dementia diagnosis. Hypertension can lead to damage to the blood vessels in the brain, making the BBB more permeable.[14] Equally, diabetes can affect the BBB through various mechanisms, including oxidative stress and inflammation.[15] In addition, prolonged exposure to high blood sugar levels can lead directly to BBB dysfunction. This can allow harmful substances from the bloodstream to enter the brain, potentially contributing to cognitive

decline and other neurological issues. These data suggested that altered BBB function maybe a causative factor in the link between these systemic diseases and dementia.

1.2 | Early-life events as risk factors for long-term neurological damage

While most of the work in this area has focused on links between adult cardiovascular health and later neurodegenerative disease, attention is turning to contributions of earlier life events to an individual's risk burden, facilitated by the natural ageing of a number of birth cohorts commenced in the 1930s and onwards. For example, analysis of data from multiple long-term birth cohorts has shown that low birth weight, low childhood intelligence quotient (IQ) and low level of education were all associated with MRI findings interpreted as SVD, independent of adult risk factors.[16] Cerebrovascular disease in adulthood has also been correlated with maternal health during pregnancy[17] and intrauterine growth restriction.[18] Preterm birth, which affects 11% of infants worldwide, has been shown to increase the risk of cerebrovascular disease, including hypertension.[19] Preterm birth also associates with increased occurrence of both haemorrhagic and ischaemic stroke in the Swedish population (born 1973–1994),[20] although an equivalent study in the Helsinki birth cohort (born 1924–1944) did not find this association.[21] Moreover, preterm birth has been linked to neurocognitive impairment in later life using a battery of tests established for identifying Alzheimer's disease.[22] As adults in these cohorts are currently aged between 50 and 70 years of age, we expect more data will be available over the next 20 years directly related to neurodegeneration.

It is currently unclear how much risk of long-term injury can be attributed to the perinatal period. In the study of Backhouse, et al.,[16] they calculated that the perinatal factors identified, for example, low birth weight and low childhood IQ, collectively contributed only 1% of the variation seen in adult measures of SVD independent of adult risk factors. Similarly, while Crump, et al.[20] showed a clear effect of prematurity on outcome, their sibling assessment also implied familial factors contribute to risk of stroke in adulthood. In considering these calculations, it is important to remember two key things. Firstly, these are very non-specific measures of altered cerebral development, with no specific associations with vascular dysfunction. Secondly, the authors of these studies deliberately separate early life events from later risk factors, and therefore do not consider the potential for early life events compounding risk with later life risk variables, such as smoking and hypertension. Data shows, for instance, that preterm birth does associate with increased hypertension in a cohort of young Swedish men.[23] What these studies do, therefore, is show that perinatal events can influence the brain over multiple decades, contributing to the risk of neurodegenerative disorders. What is required now is more specific and focused work, aimed at understanding how early life events compound risk, and whether an understanding of these will allow us to monitor risk and provide preventative therapy over a lifetime. For example, does repetitive vascular injury throughout a lifetime disrupt endothelial function in a quantifiable way, that can be measured as a biomarker of risk? Though beyond the immediate focus of this work, when considering the possibility that early-life events may sensitise the brain to vascular disease and cognitive impairment decades later, it is important to note that early life events that are associated with increased SVD[16,18,20] are also associated with delayed or impaired myelination (e.g.[24]) and may result in reduced grey matter or total brain volume.[25–27] Collectively these could limit the brain reserve capacity of an individual,[28] and therefore increase the risk of cognitive impairment or neurodegeneration. Similarly, in the context of preterm birth as a risk factor for later life cerebrovascular disease (CVD), there may be a genetic element to this risk in addition to any developmental or injury induced component. Women who have a history of giving birth preterm also have an increased risk CVD (ischaemic heart disease, stroke and atherosclerosis) in later life.[29] Additionally, conditions that predispose to preterm birth, such as pre-eclampsia, also associate with maternal cerebrovascular disease.[30]

1.3 | How do early life events directly affect cerebrovascular structure and function?

The acute effects of preterm birth on the cerebrovascular has been studied to some extent in clinical populations. CBF, measured by phase contrast-MRI of combined carotid and basilar artery blood flow normalised to brain volume, has been reported to be greater in term-born infants compared to infants born at 24–32 weeks of gestation.[31] By contrast, a more recent, though less well powered study using arterial spin labelling to measure regional CBF in very preterm infants post-birth, showed a significant increase in CBF at term-equivalent age, which was suggested to reflect an adaptation to the long-postnatal period experienced by these infants.[32] A complex set of haemodynamic responses have also been described in sheep models of preterm birth or systemic inflammation, supporting the idea that the developmental stage significantly modifies cerebrovascular function during injury. In one model, intrauterine inflammation (20 mg bolus of lipopolysaccharide, LPS, into the amniotic sac) was induced 7 days before mechanically aided preterm birth; data showed that LPS exposed foetuses had a higher carotid artery blood flow immediately following birth, with reduced cardiopulmonary response to haemodynamic challenge compared to controls.[33] In a different system, systemic inflammation produced by 1–2 μg/kg LPS i.v. resulted in a rapid change in the haemodynamic environment of foetal and neonatal sheep, with a significant decrease in arterial blood pressure and an increase in CBF occurring in foetal sheep, compared to baseline and neonatal response.[34] Both foetal and neonatal sheep showed initial vasoconstriction followed by vasodilation, though contraction was higher and longer lasting in the newborns, associated with a short-term reduction in CBF.[34]

There are numerous mechanisms by which early life events, such as those described above, may contribute to altered cerebrovascular function at a cellular level. Inflammation, a common mediator of

many injury conditions, including early life events such as preterm birth, is one of the most well studied. The BBB, present in the earliest cerebral vessels,[35] has been shown to be susceptible to inflammation-induced increases in permeability in an age-dependent manner, though not specifically related to immaturity.[36,37] These studies showed limited BBB injury in younger and adult animals to either acute systemic or intracerebral inflammation, but a large BBB breakdown at intermediate postnatal ages.[36,37] This sensitivity has been found to recapitulate in the ageing brain,[38] adding to the idea of a natural vascular senescence[39] that may be accelerated by events throughout the lifetime and contributed to altered functioning of the BBB (or increased sensitisation to injury) in ageing.[40] Not every inflammatory or otherwise injurious event in the developing brain causes breakdown of the BBB, however; for instance, alterations in vascularisation of the developing brain following ZIKA infection have been shown without substantial evidence of altered barrier permeability.[41,42] The exact nature of these changes vary with experimental model and time post injury, but collectively suggest an altered angiogenic environment in the perinatal brain following infection.

There is substantial evidence from clinical and experimental models that acute, severe brain injury associated with birth asphyxia, or other causes of hypoxia-ischaemia, results in increased permeability of the BBB (reviewed recently by[43]). In these examples, as in adult traumatic brain injury, altered BBB permeability appears to be transient, with recovery 3–7 days post-injury, and timing partially dependent on the size of the molecule used to assess permeability.[44,45] Inflammatory responses have been well described in these models,[46,47] in addition to the altered oxygen and metabolites, and are thought to be a substantial contributor to cellular injury.[47] What is less well established, is the long-term effect of these pathological processes, inflammatory or otherwise, on vascular structure and function, though two recent studies give us some insight into this. One of these, a rodent model designed to determine the mechanism of viral-induced cerebral arteriopathy,[48] showed that systemic administration of the toll-like receptor 3 agonist, polyI:C (5 mg/kg, i.p.), in juvenile (postnatal day, P, 18) mice resulted in a substantial BBB breakdown over a 3-day period.[48] Moreover, analysis showed increased collagen deposition around cerebral blood vessels within 72 h, reduced vessel number and increased lacunarity at 10 days post treatment. These data suggest that early endothelial inflammation and, in this case, neutrophil dependent BBB breakdown,[48] can result in long-term structural changes to cerebral vessels. In a different timeframe, a foetal sheep model of intrauterine growth restriction following chronic hypoxia, identified structural changes in the microvasculature 20 days after intervention was initiated, including reduced vessel number and endothelial cell proliferation.[49] These occurred together with increased BBB permeability, a 70% reduction in pericyte number around blood vessels in the white matter, and a reduced astrocyte coverage of these vessels.[49] More work is required to fully understand the long-term consequences of these early life events on the structure, function and resilience of the cerebrovascular system, but together these data suggest that events happening in the perinatal period can produce acute changes in cerebrovascular function along with short- and longer-term structural changes to the vessels.

It is important that future work determines if these early changes subsequently alter cerebrovascular responses to systemic disease, as well as contribute to cerebrovascular ageing. This is particularly important as systemic diseases that cause inflammation throughout the body (e.g. diabetes type 2) also leads to the disruption of the BBB. In the case of diabetes, the BBB disruption is at least partly a result of activation of metalloproteinases.[15] Diseases such as systemic lupus erythematosus and multiple sclerosis (MS) involve chronic inflammation and are also associated with BBB dysfunction.[50,51] Inflammatory cytokines and immune cells can activate pathways that compromise the integrity of the BBB, allowing immune cells and potentially harmful molecules to enter the brain. In many of these cases, altered BBB permeability has been detected prior to clinical disease, or in 'normal appearing' areas outside of active lesions.[52] Moreover, certain systemic infections can directly affect the BBB, for example, pathogens like human immunodeficiency virus (HIV) can cross the BBB and establish infection within the brain,[53] while circulating bacteria have a complex interaction with the BBB depending on the specific bacterial agent.[54] Ageing itself can lead to changes in the BBB, with recent work on senescence suggesting that endothelial cells in the cerebral vessels reduce nitric oxide production, become pro-inflammatory and lose tight junction protein connections (reviewed by[55]). These structural and functional alterations of the BBB, reduced autoregulation of CBF and increase access of neurotoxic substances to the brain, potentially contributing to age-related cognitive decline and neurodegenerative diseases.

1.4 | Experimental support for early vascular priming exacerbating subsequent vascular dysfunction and neurological injury

The capacity for inflammation to alter the BBB as part of systemic disease may explain findings that systemic inflammation can exacerbate neurological injury, such as dormant MS lesions, resulting in BBB disruption in situations when underlying cerebral inflammation is insufficient to produce this effect.[56,57] This response is different from the pre- or post-conditioning phenomena that have been reported by many research groups (e.g.[58–60]), where systemic inflammation in the hours before or after central inflammation can reduce cerebral injury. Instead, it appears that there may be an interaction between a cerebral endothelium that is already primed by the dormant lesion, that then reactivates quickly in response to high levels of circulating inflammatory mediators.[56] Molecular priming, such as this, is one potential mechanism by which multiple pathologies and disease states across a lifetime may contribute to the

exacerbation of neurological disease. Prolonged structural remodelling is another, though more work is required to understand the cumulative effects of vascular injury. As one pointer to this, data from studies in rats suggest that long-term alterations in BBB permeability may occur progressively after an early-life challenge.[36,61,62] In these studies, it was shown that an acute breakdown of the BBB produced by LPS induced-systemic inflammation in the newborn rat,[36] could be extended over the postnatal period by repetition of the LPS administration every 2 days up until P8.[61] The BBB remained capable of repair, with no acute alteration in permeability, measured for the small-molecular weight marker sucrose, detected either at P9 or P20. However, when assessed again in adulthood there was a significant increase in sucrose permeability compared to vehicle treated controls.[61] Electron microscopical analysis showed largely normal tight junction organisation between endothelial cells, though claudin-5 identification using light-microscopy indicated a reorganisation of the tight-junction protein in a proportion of vessels within the cortex.[62] Interestingly, these adult-acquired alterations in BBB function were also associated with the detection in adults of behavioural differences not found at earlier time points.[62]

1.5 | COVID-related future of cerebrovascular dysfunction?

One topical point for consideration on this subject is the potential effect of SARS-CoV-2 infection, producing COVID-19. There is substantial evidence that the SARS-CoV-2 virus can interact with the cerebrovasculature resulting in altered vascular tone, inflammation, oxidative stress and increased coagulation.[63] The spike protein of SARS-CoV-2 interacts with angiotensin converting enzyme 2 (ACE2), which is highly, though heterogeneously, expressed throughout the cerebrovasculature, and is at least partly responsible for these findings.[63] Clinical data from individuals exhibiting COVID-19 show a high incidence of cardiovascular or cerebrovascular events during acute disease. For example, a review of neurological sequalae associated with acute COVID-19 have shown that approximately 6% of affected individuals (primarily those in older age-groups) were diagnosed with a cerebrovascular event (most commonly ischaemic stroke), accounting for up to 60% of the neurological events detected.[64] Larger, and more recent studies support these findings, though with incidence rates of 0.5%–5% depending on the severity of COVID-19 disease.[65] Of note, risk of cerebrovascular events continues in the post COVID-19 period, with a number of studies showing increased risk of stroke or other cerebrovascular events 1–12 months following recovery.[66–68] While data in the paediatric population is more limited, an assessment of brain tissue collected during the pandemic suggests that foetal exposure to COVID-19 increases incidence of haemorrhage in the developing cortex, associated with reduced claudin-5 staining within the cerebral blood vessels.[69] In terms of potential long-term sequalae, a retrospective population study from the USA has also found an association between SARS-CoV-2 infection and stroke in the paediatric population; specifically following infection, and not associated with acute COVID-19 disease or multisystem inflammation syndrome.[70] It should be noted that this study cohort was small, reflective of the overall low risk of stroke in the population and the period of the pandemic during which data was collected (March 2020 to June 2021), and therefore more work is required to confirm these findings.

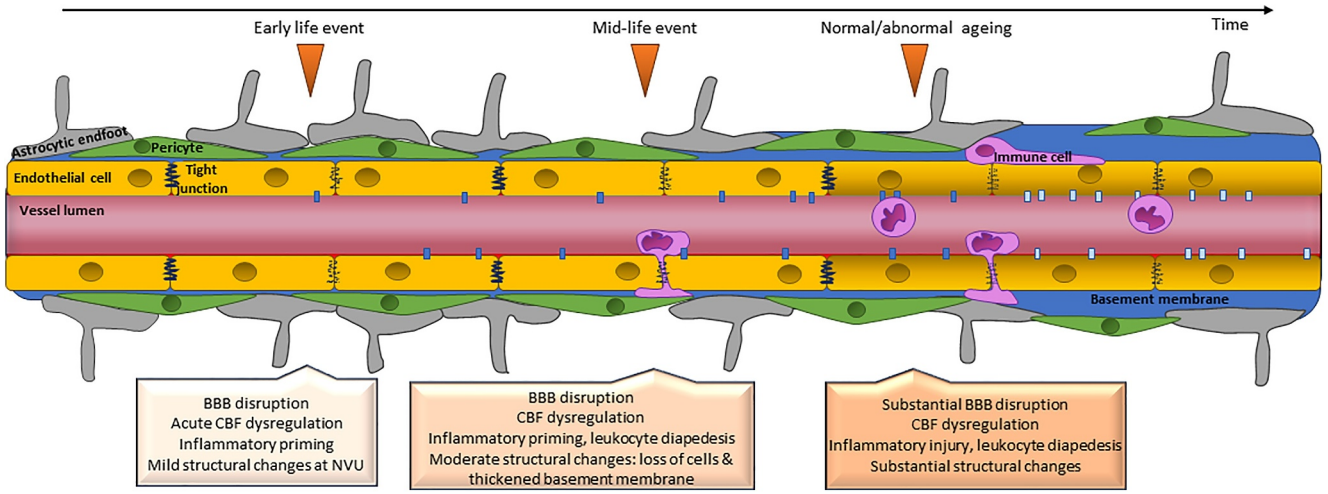

FIGURE 1 Schematic representation of accumulative damage to the cerebrovasculature across a lifetime. This schematic shows the hypothesised way early-life events may sensitise the cerebral blood vessels to augmented injury as life continues. Early events result in acute disruption, which is corrected but results in minor structural changes and endothelial molecular priming (indicated by dark blue receptors on endothelial cell surface). Mid-life events may result in further acute disruption, that is slower to repair, or more sever in the acute phase. Ageing or later life events will result in more serious responses including endothelial dysfunction (indicated by darkening of the endothelium), more substantial blood-brain barrier breakdown and diapedesis of inflammatory cells, thickening of the basement membrane and altered molecular response (indicated by light blue receptors on endothelial cell surface).

2 | CONCLUSION

Early-life events, including poor maternal cardiovascular health, preterm birth and intrauterine growth restriction can result in acute cerebrovascular dysfunction. Inflammation that occurs as part of all of these conditions produces an evolving landscape of structural and functional changes in the cerebrovascular that we are only just beginning to understand. There is accumulating evidence that these early-life events may prime the cerebrovasculature to damage in later life, increasing risk of cerebrovascular disease and neurological impairment (see Figure 1). However, data on cerebrovascular injury after early-life events is limited and typically doesn't extend beyond relatively short-term changes. Basic research and epidemiological studies are needed to understand how multiple inflammatory diseases across a lifetime may affect the cerebrovascular function. While we expect that perinatal events may increase risk of early-onset neurological events such as stroke or vascular dementia, it will be complex to separate the effects of multiple risk factors. Individuals with early-onset ischaemic stroke, for example, already have a different risk profile to those who have strokes at later ages,[71,72] with life-style factors apparently exacerbating established cardiovascular risk factors.[72] In a landscape where more children are surviving preterm birth, and where a whole population have been exposed to SARS-CoV-2 infections and its cerebrovascular sequalae, we risk a new epidemic of stroke and dementia cases in the future. Understanding, identifying and ameliorating the effects of these early life events is an essential task to prevent subsequent future disease.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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