Early Life Risk Factors for Stroke and Cognitive Impairment

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Abstract Cerebrovascular disease may present in later life with stroke or cognitive impairment and dementia, or may be silent, with changes seen incidentally on imaging or pathology. Midlife vascular risk factors such as hypertension, smoking and diabetes are well recognised. However, factors from much earlier in life may contribute to later vascular risk. In this commentary, we outline the importance of considering the whole life course in the development of cerebrovascular disease. We consider mainly factors from childhood, childhood intelligence test scores, education and socioeconomic status, which have been shown to contribute to stroke and cognitive impairment. Factors from even earlier in life, e.g. birth weight and breastfeeding also influence vascular risk factors. We discuss potential

mechanisms for the observed relationships, e.g. whether childhood IQ or access to education may influence availability of social and economic resources and adoption of certain lifestyle choices and behaviours which are beneficial to health. Other possible mechanisms behind the observed relationships include differences in brain resilience and integrity reflected in intelligence which may lead to reduced susceptibility to cerebrovascular disease or the ability to sustain a higher degree of pathology before disease becomes clinically evident. Ongoing epidemiological, data linkage, imaging and translational studies are exploring the interrelationships and underlying mechanisms, but meanwhile, it is important to take a life course perspective when considering risk factors for cerebrovascular disease.

Keywords Stroke · Cerebrovascular disease · Cognition · Education · Childhood · Epidemiology

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Introduction

Cerebrovascular disease is common at older ages [1, 2] and results in ischemic and haemorrhagic stroke, transient ischemic attacks and cognitive impairment and dementia, gait and balance disorders and psychiatric symptoms [3]. Cerebrovascular disease also manifests as small vessel disease (SVD), which can present as clinically evident stroke, but more often is clinically ‘silent’ and if advanced causes dementia and physical disabilities [4]. SVD features are detected on imaging or at postmortem [4] as white matter hyperintensities (WMH), lacunes, micro-bleeds and other features [4, 5••].

Stroke is estimated to affect 1 in 20 adults in developed countries [2]. Subclinical cerebrovascular brain changes such as WMH and silent infarcts are found in 7 and 2 % of people aged 50–69, increasing to 17 and 7.5 % in those aged 70–89

[6]. Traditionally, midlife vascular risk factors such as hypertension, smoking and diabetes have been the main focus for risk factor studies and prevention trials for stroke, SVD and cognitive impairment. However, these variables do not fully explain the risk of later life disease. One study reported the cumulative incidence of clinical stroke to be 6.8 % in those with WMH and 1.4 % in those without [7]. It is unclear why some individuals can sustain a higher degree of neuropathological change before any clinical presentations occur. It is possible that there exist individual differences in the amount of brain damage or pathology that can be tolerated before reaching a threshold for clinical expression.

It is now recognised that a person's health trajectory is shaped by experiences across the lifetime (Fig. 1). The 'Barker hypothesis' now termed the 'Developmental Origins of Health and Disease' recognises that even before birth, intrauterine influences can result in permanent changes in physiology and metabolism which have a major impact on adult chronic health conditions, particularly coronary heart disease, hypertension and diabetes [8, 9]. These can be modified by later life experience; therefore, it is important to take a life course perspective when considering risk factors for cerebrovascular disease. Here, we outline the relationships between two main childhood factors—cognition and education—and later life stroke and associated cognitive impairment.

Lifelong Effects of Cognition on Cerebrovascular Disease

Childhood Cognition and Risk of Stroke

Childhood cognitive ability is associated with numerous health outcomes including longevity [10], general health [11] and several specific chronic health outcomes such as cardiovascular disease [12, 13], respiratory diseases [14] and stroke [12–16]. Furthermore, higher childhood intelligence is associated with better cognitive ability in older adulthood [17] and may influence later cognitive decline [18], perhaps by influencing peak adult cognitive function and/or the rate of cognitive decline [19].

Childhood intelligence has been identified as an important factor in determining the effect of age-related changes in the brain and development of overt cerebrovascular disease. Higher childhood IQ is associated with higher cognitive reserve, fewer WMH [20••] and better white matter integrity [21, 22]. For example, Shenkin and colleagues [22] found that scores on cognitive tests at age 11 and scores on the National Adult Reading Test (NART), a marker of premorbid cognitive function, correlated with diffusion tensor imaging parameters in the centrum semiovale at age 80. Pathological brain changes such as WMH have also been associated with childhood

Fig. 1 The life course perspective of the risk of cerebrovascular disease and stroke

cognitive ability [20••]. A longitudinal study by Valdèz Hernández and colleagues [20••] reported an inverse relationship between age 11 IQ and WMH load around age 73. The strength of this relationship increased for those with evidence of previous clinical or subclinical stroke, with the volume of WMH almost doubled compared with those without stroke, independent of vascular risk factors.

How well does childhood cognitive ability predict later stroke? Some studies find that children with lower cognitive ability have a higher risk of stroke [12, 15, 23], although other studies found no such association after controlling for other risk factors [13, 16]. This is perhaps due to the difficulty of classifying stroke retrospectively and without imaging or lack of availability of information regarding childhood cognitive scores. However, the NART [24], The Mill Hill and the Wechsler Test of Adult Reading (WTAR) [25] which assess crystallised intelligence can be used to measure premorbid IQ. These measures are built on the assumption that reading ability, an aspect of crystallised intelligence, remains constant regardless of age or damage to the brain [26] and scores in old age have been shown to correlate highly with childhood IQ [27]. Furthermore, poor performance on tests of crystallised intelligence has been associated with cognitive impairment following stroke [28].

Interpretation of these studies may be difficult due to differing study designs, populations and measurements. Additional residual confounding by other factors that may affect childhood IQ and stroke must also be considered. These factors include genetics [29], early life social, environmental and nutritional factors [30, 31•, 32], education [23] and socioeconomic status (SES) [15]. It is important to consider all of these and how they relate to one another across the life course when considering risk of disease.

Education and Risk of Stroke

Several small studies have demonstrated the relationship between education and neuropathological changes associated with cerebrovascular disease [33, 34•]. For example, people with lower levels of education have a higher frequency of cerebrovascular lesions and SVD [34•] including infarcts, lacunes and white matter rarefaction [33]. However, it is unclear whether these studies adjusted for health-related behaviours such as smoking and alcohol use. This is an important factor to consider when interpreting results from such studies especially given the complex interrelationships between risk factors for cerebrovascular disease.

Education is inversely associated with risk of stroke [23]. Lawlor [23] reported that for every additional category of education, females were 41 % and males were 16 % less likely to have a stroke. After adjustment for other early life factors such as IQ, this decreased slightly to 35 and 10 % for females and males, respectively.

Education has been associated with events following stroke such as cognitive impairment [35] and mortality [31•, 35]. Long educational history has been associated with lower frequency of cognitive deficits and improved long-term survival in patients following stroke after adjustment for age, WMH and stroke severity [35]. Another larger study of stroke patients from across Sweden [31•] reported that university education was independently and positively associated with survival following the first ever stroke. This relationship was consistent across gender, age and time period after stroke and independent of stroke severity.

Educational attainment is strongly related to both cognitive ability and SES [36] which in itself has been associated with cerebrovascular disease risk. A systematic review of nine studies reported a strong relationship between childhood socioeconomic circumstances and risk of stroke in later life [37]. The association between education and SES means that education is often used as an indicator of SES; however, their relationship may be bidirectional, for example, unfavourable socioeconomic circumstances can restrict opportunities for or access to higher education.

The Relationship Between Education and Childhood IQ

Childhood IQ and educational attainment are closely linked [38], and several researchers have suggested that education may be a surrogate for cognitive ability. IQ may influence educational choices with more intelligent people accessing higher or further education. Higher IQ may also lead to more educational success [38], better employment opportunities and access to other socioeconomic benefits associated with achieving better health. Adjustment for education [12, 16] and other socioeconomic factors [16, 23] in the intelligence-health relation has largely shown a consistent and strong attenuating effect. Conversely, controlling for intelligence in the education-health (including stroke) relationship had little effect [39].

Individuals with contrasting levels of education and IQ may provide a unique opportunity to separately assess these variables in relation to health. Link and colleagues [39] reported that positive health outcomes were more strongly predicted by higher levels of education than higher levels of intelligence. This suggests that education may have a positive effect on improving health outcomes regardless of IQ.

However, the relationship between these variables is complex. It is plausible that education may represent at least a partial proxy to childhood cognitive ability, as variance in educational outcome is to a substantial extent a reflection of differences in mental ability. However, it can also be argued that education exerts at least a small amount of influence on health independent of the effect of childhood mental ability [39] as indicated by the apparent protective effect of exposure to minimal amount of schooling on cerebrovascular disease risk [34•].

Cognitive Decline Prior to Stroke

The interrelationships between lifetime cognition and stroke are complex. Cognitive impairment may be a very early and subtle indication of cerebrovascular disease [40]. Impaired cognition predicts later stroke risk, e.g. impaired executive function is associated with higher 10 year stroke risk [40]. Furthermore, impaired cognitive function in the few years before stroke can predict the onset of the first stroke better than conventional vascular risk factors, particularly in those over 85 years of age [41•]. A score of less than 24 on the Mini Mental State Exam (MMSE) was associated with a 35 % relative increase in stroke, comparable to the risk associated with a prior stroke [42]. A possible explanation for this is that cognitive impairment is an indication of subclinical vascular disease which may later result in stroke [43]. Consequently, selective cognitive tests may be a promising and sensitive screening tool for those most at risk of stroke or SVD but this requires validation. However, it is difficult to rule out reverse causation as it is tenable that unidentified risk factors or undiagnosed early cerebrovascular disease may be responsible for cognitive decline. One way to eliminate reverse causation is to measure risk factors in childhood, before development of mid-life illness such as hypertension and diabetes which can also reduce cognitive ability [44, 45]. Longitudinal studies will also allow consideration of the possibility that impaired cognition is due to lifelong poorer cognitive function, rather than new cognitive impairment.

Cognition Following Stroke

Both clinical stroke and SVD are associated with an increased incidence of cognitive impairment and dementia [46]. Vascular cognitive impairment is defined by evidence of cerebrovascular disease as well as impairment in at least one cognitive domain assessed using validated measures [47–49]. Vascular dementia (VaD) is the second most common form of dementia after Alzheimer's disease and both may increase with the growing ageing population [50]. A diagnosis of VaD will be made when two or more cognitive domains are affected, associated with functional impairment [51]. The degree of impairment is determined by risk factors including increasing age [52], previous or recurrent strokes, WMH, hypertension, smoking, diabetes and atrial fibrillation [53]. However, as with risk of stroke, these conventional risk factors do not fully explain individual differences in occurrence of VaD or cognitive impairment.

In a systematic review of 30 patient cohorts ($n=7511$), the prevalence of post-stroke dementia varied from 7 to 40 % [53]. This variance may be in part due to whether the first ever or recurrent stroke was considered and also whether those with pre-stroke dementia were included. Pre-stroke dementia

affects between 9 and 14 % of stroke patients, and those studies which excluded patients who had dementia before the stroke reported much lower prevalence than those who included such patients [53]. This provides support that a proportion of those who develop cognitive decline following stroke have some form of cognitive impairment before, and the stroke itself may trigger a decline in cognitive function. It is becoming increasingly recognised that it is important to consider pre-stroke cognitive impairment/dementia in the years leading up to stroke as it may affect cognition following stroke. However, as people often present suddenly with stroke, it can be difficult to measure pre-morbid cognition. Studies are using measures such as The Informant Questionnaire on Cognitive Decline in the Elderly [54] (IQ-CODE) to account for this. However, this measure can also be difficult to administer as it requires an informant to be available. The use of such measures will help to (a) control the assessment of post-stroke cognitive impairment for undiagnosed pre-stroke cognitive impairment and (b) help to address the recent observation that declining cognition in later life is itself a risk factor for stroke [42]. In other words, cognitive decline may lead to stroke and stroke leads to cognitive decline, in later life—the extent to which both are influenced by early life exposures, and whether these act synergistically on the risk of stroke and of cognitive decline in later life, remain to be determined.

Mechanisms Behind Observations

Several reasons have been proposed for the associations between early life factors and cerebrovascular disease and subsequent cognitive impairment.

(1.) *Behaviour and lifestyle*

Across the lifespan, the influence of behaviour and lifestyle on later life disease begins with genetic and parental exposures prior to birth. The socioeconomic status of an individual's parents can influence their exposure to risk factors for cerebrovascular disease and stroke both prior to birth and throughout childhood [55•]. These risk factors include poor nutrition, low birth weight [9], exposure to smoking [56] and decreased access to healthcare and education [39]. These factors in turn can influence childhood cognitive ability and level of education achieved. Education can shape access to social and economic resources and exposure to environments and occupations that may protect against certain health problems [39]. Similarly, intelligence can influence self-management of health and health-related information either as a preventative strategy or to address an existing problem [57]. Furthermore, intelligence may influence adoption of certain behaviours that are conducive to health such as level of

exercise, diet and alcohol consumption which influence risk of cerebrovascular disease. This is illustrated in the observation that individuals with higher childhood IQ are less likely to smoke in adulthood [58] and more likely to stop smoking by the age of 30 [11]. Higher risk of stroke, as measured by the Framingham stroke risk profile, predicts cognitive decline in multiple domains from midlife [59].

(2.) *Brain Integrity and Cognitive Reserve*

In addition to influencing behaviour and lifestyle, there is accumulating evidence that education and early life IQ act as a marker of neural integrity and some evidence that poor integrity of cerebral white matter may predict vulnerability to stroke and cognitive decline.

General cognitive ability is a lifelong, stable trait and therefore factors that determine or contribute to this are likely to begin in childhood. These overlapping factors may help explain the association between childhood intelligence and accumulation of silent cerebrovascular disease, e.g. white matter changes and vulnerability to stroke and cognitive impairment [60]. Cognitive information processing speed has long been recognised as a correlate of general intelligence and indicative of cognitive decline [61], and efficient information processing is thought to rely on the integrity of interconnecting white matter tracts [60]. For example, information processing speed has been shown to mediate the relationship between white matter tract integrity and general intelligence in the seventh decade [62].

White matter tract integrity can be measured using magnetic resonance diffusion tensor imaging (DTI) and can be used to assess white matter damage as a result of ageing or disease [63]. It provides two quantitative parameters, the mean diffusivity ($< D >$) and fractional anisotropy (FA) which are used to indicate the amount of tissue damage evident in an individual. Fractional anisotropy has been shown to fall linearly with age, particularly in the frontal regions [64]. Cortical disconnection of these tracts can cause disruption of neurocognitive networks, and this has been proposed as a possible mechanism for the cognitive changes which underpin cognitive ageing [64].

Both education [65] and cognitive ability [21] have been associated with white matter integrity. Education has been found to be the main predictor of fibre tract integrity in several brain areas with those with higher levels of education having more richly connected fibre tracts [65]; however, this was not corrected for prior IQ. Longitudinal studies have reported that white matter integrity in the centrum semiovale at age 83 correlates with age 11 IQ and white matter integrity along with processing speed accounted for 85 % of age 83 general cognitive ability [21]. What is less certain is the degree to which

lifetime brain integrity protects against cerebrovascular disease in later life and whether any such association can be influenced by exposure to more or less education.

Early life factors may influence the development of stroke and cognitive impairment through their effect on cerebrovascular disease markers such as WMH [20•, 34•, 66]. Education and cognitive ability may provide a protective advantage in two ways; firstly, they may provide resilience against the development of white matter changes as shown by the inverse relationship between WMH and age 11 IQ [20•]. Secondly, early life factors may provide resilience to the effects of WMH by increasing the threshold of pathological load required in order to develop clinically evident disease, perhaps by reducing the impact of cerebrovascular pathology on cognition [34•, 66]. Education may modify the relationship between white matter changes and cognition [34•, 66]. Among those with low levels of education, the presence of WMH [66] or lacunar infarcts [34•] are associated with lower cognition. However, for those with more years of education, the likelihood of cognitive impairment from WMH and lacunar infarcts has been shown to be much lower [34•, 66]. These mechanisms are often referred to as the theory of cognitive reserve which proposes that greater brain integrity can protect the brain from negative neurological sequela through both ‘active’ and ‘passive’ pathways [67]. While passive cognitive reserve relates to histology and brain size, active reserve refers to the ability of redundant pathways to take over following damage to the brain [67].

Implications

Stroke and dementia are common, serious health conditions which have substantial cost implications for the national economies and cause a significant amount of distress and disability to patients and carers. Research into early life risk factors for cerebrovascular disease may help inform future interventions and planning of health and educational services and social policy to target those most at risk. Identifying risk and resilience factors in childhood will help highlight the lifelong level of vulnerability and guide development of prevention strategies that could be implemented from early childhood onwards.

Conclusion

Stroke increases the risk of, and is a major cause of, cognitive impairment or dementia; cognitive decline increases risk of stroke and is associated with ‘silent’ cerebrovascular disease features. Early life factors such as better childhood cognitive ability and education may protect against later risk of cerebrovascular disease and dementia, although the association may

be confounded by other genetic or environmental factors. Childhood cognitive ability and education may influence health behaviours and access to socioeconomic resources beneficial to health. Additionally, they may increase brain integrity and resilience leading to reduced susceptibility to cerebrovascular disease or to the ability to withstand higher pathologic load or moderate the relationship between SVD and clinical expression of disease. Education and cognitive ability are closely associated and education may be at least a partial proxy for IQ. Planned studies of clinical and population cohorts will help to understand these interrelationships and underlying mechanisms. This could then lead to the potential for exploring whether the risk factors early in life might be modifiable. Interventions to affect early life education or to preserve later life cognition are complex and may require changes in social policy or public health strategy. However, many strategies that could have a positive impact on cerebrovascular disease are those that would be priorities for government policy for other reasons. It is essential that the whole life course is included when considering risk factors for the development of stroke and post-stroke cognitive impairment.

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Compliance with Ethics Guidelines

Conflict of Interest EV Backhouse, CA McHutchison, V Cvorovic, and SD Shenkin declare that they have no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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