The Puzzle of Predicting the Impact of Brain Infarcts on Cognitive Impairment in the Aging Brain

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See related article, pages 677–682.

Several studies have demonstrated that cerebral infarcts increase the risk for cognitive impairment, dementia and poststroke depression.1–3 The patterns by which infarcts cause cognitive impairment are not entirely understood. Potential explanations include the location and number of infarcts. Infarcts disrupting the cerebral circuitry may impact function on specific cognitive abilities, whereas infarcts affecting the frontal-subcortical circuits are associated with memory, information processing, and executive function.4–6

In this issue of Stroke, Sacyznski and colleagues investigate the role of infarct number and location on performance in 3 cognitive domains—processing speed, memory, and executive function—analyzing data from the population-based Age Gene-Environment Susceptibility-Reykjavik Study (AGES-Reykjavik). The authors hypothesize that the combination of multiple infarcts in multiple locations is a stronger predictor of cognitive impairment than either infarct alone.

Assessing the impact of quantity of infarcts on cognitive function, it is shown that infarcts in multiple locations had slower processing speed, poorer performance in memory, and executive function. Interestingly, participants with multiple infarcts in a single location did not perform significantly different from those with no infarcts after model adjustment. The authors go on demonstrating that either the cortical or subcortical locations of infarcts alone were associated with impaired memory function. Investigating the combination of cortical and subcortical and cerebellar infarcts on cognitive impairment, the authors found that combined cortical and subcortical infarcts impacted on slower processing speed and memory function, whereas a combination of cerebellar and subcortical infarcts was associated with slower processing speed. Finally, infarcts in all 3 brain locations were associated with slower processing speed. In summary, the authors showed that those with multiple infarcts in multiple locations had the lowest performance on all 3 cognitive abilities. These results were independent of white matter lesions, brain atrophy, cardiovascular comorbidities, and depressive symptoms.

Do the results of this study indicate that the aging brain lacks sufficient compensatory mechanisms contributing to plasticity and repair after infarcts in case of a higher load of infarcts in multiple locations rather than the close correlation between cognitive impairment and the effects of the circumscribed brain damage through the actual single infarct in one location? If so, then it is important to evaluate other factors that may contribute to reduced capacity of the brain to compensate for cognitive impairment.

Factors such as aging, neuroinflammation, white matter lesions (WML), and depression that have the ability to weaken those brain circuitries and to make the brain more susceptible to further brain damage after infarction may share a similar vascular pathophysiology with infarction and have similar effects on cognitive impairment. Therefore, the presence of those risk factors before the occurrence of brain infarction may significantly contribute to neuropsychological impairment after infarction.

Firstly, a number of age-related functional changes in the brain may contribute to a decrease in capacity of the brain to compensate for cognitive impairment. More specifically, normal aging is accompanied by characteristic decrements in memory performance.7,8 The capacity to deliberately acquire and retain new information (declarative episodic memory) is often impaired during aging indicating the use of less-efficient encoding and retrieval strategies. The age-related impairment in memory has been found to covary with other measures of frontal lobe function, the Wisconsin Card Sorting Test, and verbal fluency.8,9 There is also evidence that with aging, the frontal lobe undergoes greater reductions in volume and in resting functional activity than do other brain areas. In addition, there is evidence linking impaired implicit memory to age-related frontal lobe dysfunction.10

Secondly, increasing evidence suggests that common pathways are emerging that link many normal aging inflammatory processes with age-related diseases such as cognitive decline, Alzheimer, cancer, diabetes and cardiovascular disease.11 During normal aging a progressive neuroinflammatory state builds in the brain involving astrocytes and microglia, the primary cellular components of neuroinflammation. Recently, it has been suggested that increased proinflammatory cytokines are involved in aging processes. One of the most consistent findings in gerontological surveys of cytokines is an age-dependent increase in interleukin 6 (IL-6) levels.12,13 In a longitudinal study, high initial IL-6 concentrations in the plasma of older individuals were predictive of subsequent disability, including cognitive impairment.14 Other cytokines appear also involved during aging as recently show in a study.
by this group: increased levels of the IL-8 (chemokine) were consistently related with decreased cognitive performance in memory, cognitive speed, and motor function in a general aging population.15

Thirdly, WML should be considered as an important factor for the decreased capacity of the brain to compensate after brain infarctions. WML increase in prevalence with age and possibly have a vascular etiology16 involving inflammatory processes of the arterial wall,17–19 which may also be involved in the development of WML.20 A number of previous studies with few exceptions21 have shown that increased WML load correlates with cognitive impairment,22,23 but studies disagree as to the size of the effect and the cognitive domains involved.21 Among the cognitive functions that seem to be affected by WML, speed and attention appear particularly impaired,24–26 although impairment in memory, executive and motor function also have been reported.22,25,27,28 In a recent study we showed that the combined occurrence of large WML and lacunar infarctions predicted the worse outcome in cognitive abilities than the presence of these MRI characteristics in patients with depressive disorders.30,31 These deficits relate to several aspects of cognitive function such as visuo-spatial functions, attention/concentration, memory and executive functions.32 Persistent cognitive deficits in depression could be explained either as a consequence of persistent subacute depression or as a consequence of irreversible neuronal modifications.33,34 In a recent study we reported a link between depression and processing speed, visuo-motor and executive abilities in normal older adults supporting the subcortical-frontal circuit dysfunction model of depression.35 There is growing evidence that processing speed and executive functions are strongly mediated by the prefrontal cortex and the striatum.36,37 When these brain areas result in cognitive impairment in depression, the same areas, which are often affected by infarctions, dispose of a lesser degree of capacity for compensation even before a brain infarction occurs in these areas.

Fourthly, neuropsychological deficits are common characteristics in patients with depressive disorders.30,31 These deficits relate to several aspects of cognitive function such as visuo-spatial functions, attention/concentration, memory and executive functions.32 Persistent cognitive deficits in depression could be explained either as a consequence of persistent subacute depression or as a consequence of irreversible neuronal modifications.33,34 In a recent study we reported a link between depression and processing speed, visuo-motor and executive abilities in normal older adults supporting the subcortical-frontal circuit dysfunction model of depression.35 There is growing evidence that processing speed and executive functions are strongly mediated by the prefrontal cortex and the striatum.36,37 When these brain areas result in cognitive impairment in depression, the same areas, which are often affected by infarctions, dispose of a lesser degree of capacity for compensation even before a brain infarction occurs in these areas.

Finally, the reported risk factors taken together interact with brain circuitry and subsequently negatively with cognitive abilities during normal aging processes and neurodegenerative or cerebrovascular diseases such as infarctions. The presence of those brain damaging factors might or might not contribute to cognitive impairment alone; however, they may act in additive or multiplicative ways together with brain infarctions. Since some of those factors are highly interdependent, such as neuroinflammation, depression, cognitive impairment, and possibly WML, individuals with combined risk factors are at an increased risk of cognitive impairment after brain infarction regardless of or particularly because of multiple numbers of infarctions in multiple locations.

In conclusion, the factors aging, neuroinflammation, WML, and depression have the potential to increase the brain’s susceptibility for cognitive impairment after brain infarction. Despite the difficulty to study complex and multivariate interactions of all of those factors simultaneously in single studies, it appears to be important to at least consider and discuss these factors in the complexity of brain damage after infarctions. Equally important, on an individual case basis the identification of all contributing factors is essential in order to improve management of modifiable factors such as depression and neuroinflammation among affected patients.

Disclosures

None.

References


Key Words: neuropsychology ■ stroke management
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Stroke. 2009;40:667-669; originally published online January 8, 2009;
doi: 10.1161/STROKEAHA.108.534230

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