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Emerging Risk Factors in Women

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Abstract

Stroke is a major cause of long-term disability and death for women in this country, with recent evidence suggesting higher rate of stroke in midlife women than men, as well as higher lifetime risk of stroke for older women. Several recent papers highlight emerging areas of interest for research on risk factors for stroke in women. This article will review data published in the last year, focusing on three potential risk factors that may partially explain these differences between men and women: central adiposity and related adipocytokines, endogenous sex hormones, and depression.

Introduction

Stroke is a major cause of long-term disability and death for women in this country. The lifetime risk of stroke for women age 55–75 years is approximately 20%, which is notably higher than that for men (14–17%).[1] Recent data suggest that stroke rates in midlife women have tripled in the past two decades (successive NHANES cohorts between 1988–1994 and 1999–2004), while the rates in men stayed flat.[2] This article will highlight several areas of emerging interest in research on risk factors for stroke in women: central adiposity and related adipocytokines, endogenous sex hormones, and depression.

Central adiposity and adipocytokines

Obesity is associated with a more than 2-fold increased risk of ischemic stroke in women.[3] In recent analyses in ARIC, degree of obesity, defined by body mass index, waist circumference, or waist-to-hip ratio, was a significant risk factor for ischemic stroke regardless of sex or race.[4] Central adiposity, reflecting increased volume of more metabolically active visceral fat, may play an especially prominent role. Recently, Towifighi and colleagues found that increased waist circumference was the only independent stroke risk factor explaining the increasing stroke rates among women in the past two decades.[2] Thus, central adiposity may play a particularly important role in stroke risk in women.

Adipose tissue secretes a variety of cytokines, including adiponectin, hepatocyte growth factor and others, that influence insulin resistance as well as inflammation and may affect cardiovascular risk. Hepatocyte growth factor (HGF) is an adipocytokine which also has potent angiogenic characteristics, with activation leading to cell proliferation and neovascularization.[5] Circulating HGF levels were higher among acute ischemic stroke patients,[6] than controls. In a recent study of 972 ischemic stroke cases within the Women's Health Initiative (WHI) Observational Study, HGF levels were significantly higher in cases than controls (p=0.003).[7] After adjustment for body mass index and other cardiovascular risk factors, women in the highest HGF quartile had a 39% increased risk of incident ischemic stroke. Results persisted after adjustment for CRP.[7]

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Other adipocytokines have received interest as well. Two adiponectin gene variants (rs266729 and rs182052) were associated with decreased risk of ischemic stroke in men, independent of diabetes.[8] However, in recent analyses from the WHI, no association between high molecular weight (HMW) adiponectin and incident ischemic stroke in women was observed, despite associations between adiponectin and multiple cardiovascular risk factors.[9] Further research on potential mediators of the risks associated with central adiposity may lead to new insights to explain sex differences in risk of stroke, as well as biologic mechanisms by which adiposity increases the risk of stroke. From a public health standpoint, additional efforts to prevent obesity are needed to aid in stroke prevention.

Endogenous estrogens

Several lines of indirect evidence support a relationship between estrogens and cardiovascular disease including ischemic stroke; however, actual direct evidence is scant. Exogenous estrogen use has been consistently associated with at least a 40% increased risk of ischemic stroke in both observational studies[10] and randomized trials.[11–13] Although estradiol levels have not been associated with total CVD in prospective studies of women;[14–16] none had sufficient power to examine stroke in detail. In the Rotterdam Study, a 1 standard deviation increase in total estradiol levels was associated with a 2-fold increase in vascular dementia in older women.[17]

In the first study reporting the association of endogenous estrogens and stroke in women, estrogen levels were examined among 9,704 women age 65 or older in the Study of Osteoporotic Fractures. In analyses adjusted for age, a linear relationship with ischemic stroke was seen, with those in the highest free estradiol index (FEI) having a more than 2-fold increased risk of ischemic stroke. Adjustment for lipids, CRP, and other cardiovascular risk factors, attenuated the odds ratio to 1.23 in the highest quartile.[18] There was a suggestion of a possible interaction by waist circumference (p=0.08), with women with both high FEI and high waist circumference having markedly higher risks.[18] The possible interaction of estrogens and central adiposity deserves further study. Additionally, research on endogenous estrogens may improve understanding of how estrogen-modifying therapies may affect stroke risk.

Depression and antidepressant medications

Rates of depression are two-fold higher in adult women than in men, throughout the lifespan, regardless of race.[19] Depression is strongly linked to incident CHD;[20] however, data for stroke are more limited, particularly for stroke type.

Several prior studies have examined depression and risk of stroke in women. In the largest of these among women in the WHI, women with depression but no history of CVD were not at increased risk of stroke, while those with a history of prior cardiovascular disease were at a 45% increased risk of stroke.[21] In another study of elderly men and women, depressive symptoms in participants with preexistent cardiac disease, but not in those without, were associated with increased risk of stroke.[22] A 2007 meta-analysis found a pooled estimate for total stroke of 1.43 (95% CI: 1.17–1.75), but with substantial heterogeneity between studies and a lack of data by gender.[23]

In a recent provocative paper, Smoller et al examined the impact of new antidepressant use on risk of stroke among 136,293 women in the WHI who were not using antidepressant medications at baseline. Those who reported SSRI use at the first follow-up visit were at 55% higher risk of total stroke, but no increased risk of CHD.[24] Selective serotonin reuptake inhibitor (SSRI) use was associated with 45% increased risk of stroke risk. A prior case control study within a managed care database found a 24% increased risk of stroke among those on SSRIs, with similar risks for other antidepressants.[25]

Multiple mechanisms might link depression and risk of stroke. Depression has been linked to increased inflammation and higher resting sympathetic tone. Women with depression may have reduced medication compliance and poorer health behaviors due to co-existing depression. Other comorbidities, such as diabetes, cardiovascular disease and sleep disorders are more common among depressed women. Finally, depression, particularly new onset depression in older women, may be a manifestation of subclinical vascular disease ("vascular depression"). It is possible that antidepressants might have untoward effects on risk of stroke, such as the known effects of SSRI's on platelet inhibition. However, such platelet effects would have been expected to reduce the risk of ischemic stroke, while increasing the risk of hemorrhagic stroke. Alternatively, the increased risk associated with antidepressant use might be attributable to antidepressants being a marker of depression severity which may lead to poor compliance with medications as well biologic effects. If risk from depression is due to its manifestation of subclinical vascular disease, then SSRI's would be expected not to influence risk and more aggressive cardiovascular risk factor management in these women may be warranted. Further research is needed to investigate the causal pathways that link depression and cerebrovascular disease and to test therapies that might reduce associated risk.

Conclusion

The last year has brought many exciting developments in risk factors for stroke in women. Further research regarding the role of central adiposity and risk of stroke in women is needed, particularly identifying biologic mediators that mediate this risk which may open new pathways for risk reduction. Efforts to replicate the findings for hepatocyte growth factor, endogenous estradiol and depression are needed. These risk factors may offer insights into biologic stroke mechanisms as well as potential modifying treatments.

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